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**Alteration in taste perception and its relationship with nutritional status
and quality of life in patients with advanced cancer**

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Submitted for the degree of Doctor of Philosophy

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ABSTRACT

Conducted within the hospice setting, this unique study assessed the prevalence of altered taste perception and its potential relationship with nutritional status in a group of 56 advanced cancer patients who had not received any recent radiotherapy or chemotherapy, compared to 46 age matched healthy controls. An assessment was made of the impact of altered taste perception on quality of life in this group of cancer patients. Taste perception was objectively measured using the International standard for sensory appraisal (ISO1991) and nutritional status assessed using upper arm anthropometry, bioelectrical impedance analysis, weight and hand grip dynamometry. A 3-day weighed intake technique was used to estimate dietary intake, and quality of life assessment was based on the Hospital Anxiety and Depression scale (Zigmond and Snaith, 1983). Results indicate that cancer patients exhibited lower 'bitter' thresholds (increase bitter taste sensitivity) compared to age matched controls an effect which was not related to tumour type. Results of this study also highlight the impact that changes in taste perception have on quality of life, which is pivotal in the appropriate management of altered taste perception in palliative care. Heightened olfactory perception was also evident in cancer patients exhibiting heightened gustatory perception. Biochemical analysis suggests that Tumour Necrosis Factor α and associated acute phase response may be associated with increased bitter taste sensitivity. Within the cancer group, heightened bitter perception was associated with a reduced protein intake. These results have demonstrated that in a terminally ill group, dietary management should focus on altered taste perception, aiming to maximise quality of life. Based on these results, a 4-week intervention was undertaken using omega 3 fatty acid (fish oil capsules) in a subsequent group of advanced cancer patients, aimed at manipulating the acute phase response and TNF α production. This demonstrated no changes in taste perception. However, the intervention was associated with attenuation of

weight loss and an alteration in fatty acid composition of lipid membrane. These preliminary results suggest the value of further studies to investigate the effects of omega 3 fatty acids on taste perception and other associated symptoms in cancer patients. Moreover, the challenges to recruitment and retention of patient in studies in the terminally ill are highlighted.

LIST OF ABBREVIATIONS

AMA	Arm Muscle Area
AMC	Arm Muscle Circumference
BIA	Bioelectrical Impedance Analysis
BMI	Body Mass Index
BMR	Basal Metabolic Rate
cm	Centimeters
CRP	C-Reactive Protein
CT	Chorda Tympani
DHA	Docosahexaenoic Acid
ELISA	Enzyme linked immunoassay
EPA	Eicosapentanoic Acid
FM	Fat Mass
g	Gram
HAD Scale	Hospital Anxiety and Depression Scale
IBW	Ideal Body Weight
IL1 α	Interleukin-1 alpha
IL1 β	Interleukin-1 beta
IL-6	Interleukin-6
kg	Kilogram
kcal	Kilocalorie
kHz	Kilohertz
LBM	Lean Body Mass
m	Meters

M	Moles
mM	Millimoles
MJ	Mega joules
ml	Millilitres
MUAC	Mid Upper Arm Circumference
mg	Milligram
n-3	Omega-3
ng/l	Nanogram/litre
nm	Nanometers
QOL	Quality of Life
q.d.s.	Four times a day
pg/ml	Picogram per millilitre
see	Standard Error of the estimate
sem	Standard Error of the Mean
TBW	Total Body Water
t.i.d.	Three times a day
TNF α	Tumour Necrosis Factor alpha
TSF	Triceps Skinfold Thickness
μ g	Micograms
μ mol	Micromoles
μ A	MicroAmps
VAS	Visual Analogue Scale
Ω	Ohms

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DECLARATION

I declare that the work contained in this thesis is original. I have been solely responsible for the organisation and co-ordination of the study contained herein, aswell as all aspects of data collection and the analysis of results, unless otherwise stated.

Ruth Pattison
Research Student

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ABSTRACTS AND PUBLICATIONS

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RM Pattison, RA Richardson, H Dougan, HIM Davidson (1997) Biochemical correlates of altered taste perception in patients with advanced cancer *Clinical Nutrition* 16, (2) 29

Paper Entitled: Chemotherapy and Immunonutrition

Presented: XVIII European Society for Parenteral and Enteral Nutrition, Geneva, 1996

To the memory of Dad

CHAPTER 1

Introduction

CHAPTER 2

Methods

CHAPTER 3

Prevalence and magnitude of alterations in taste perception in patients with advanced cancer

CHAPTER 4

Impact of altered taste perception on quality of life

CHAPTER 5

Investigation of the nutritional status of patients with taste changes

CHAPTER 6

Impact of altered taste perception on dietary intake

CHAPTER 7

**Association between biochemical parameters and altered taste perception
in patients with advanced cancer**

CHAPTER 8

Omega 3 fatty acid intervention and alteration in taste perception

CHAPTER 9

Summary, Conclusion and Further Considerations

1.1 Introduction

In recent years the management of patients with advanced cancer has seen a shift from care in the acute setting to the hospice where quality of life (QOL) is of prime concern (Cohen and Mount, 1992). Palliative care focuses on the management of disease associated symptoms, aiming to maximise QOL of patients (Bruera, 1992). To achieve this aim, nutritional support is an important component of the multidisciplinary approach used in the palliative management of malignant disease (Bruera and Fainsinger in Doyle *et al*, 1993).

Conducting research in a dying population is an activity, which in itself has the potential to impinge on the QOL of patients. Indeed, several researchers are of the opinion that patients with advanced disease, should share remaining time with family and/or friends without the intrusion of new treatment modalities (Scanlon and Fleming, 1989). A balance between research objectives and medical challenges in this clinical setting is required. In addition, there is the QOL of researchers working in an emotionally stressful environment that may also require support.

In recent years, the majority of clinical research conducted in hospices have been retrospective in nature and are limited due to ethical considerations and difficulties in recruiting patients who are terminally ill. However, without prospective studies being performed, advances in care in improving QOL can not be assessed following intervention. A limited number of prospective longitudinal studies have been performed in palliative care and as a result there is limited information regarding possible recruitment and retention difficulties encountered in

these studies for example, a patient's condition may deteriorate or change and new symptoms may present within a short period. This in turn may necessitate alterations in treatment regimens that may exclude patients from participating in a study (McQuay and Moore, 1994). Despite these difficulties, it is important to acknowledge that research in this area can add a positive dimension to palliative care, for example, patients may gain comfort from the knowledge that others in the future may benefit from research studies (MacDonald, 1995).

Palliative care involves the management of symptoms of advanced cancer such as cachexia, which is present in the majority of end-stage cancer patients. However, many research trials have failed in reversing cachexia weight loss mainly due to the lack of effective treatment strategies. However, the complex mechanisms of weight loss in cancer may explain why there are such difficulties in dietary intervention programmes. Symptoms of the cachexia syndrome include altered chemosensory function, altered food preferences and associated with altered metabolism (DeWys 1974; Shaw 1992).

The identification of factors that contribute to nutritional related symptoms are clearly important because of the negative impact that the resulting anorexia and malnutrition have on QOL and social interaction (Tchekmedyian *et al*, 1990). In patients with advanced cancer, who may already be nutritionally compromised by the presence of disease, an alteration in food intake may disproportionately affect QOL. Malnutrition and associated apathy and depression have been associated with a negative effect on appetite (Tait and Aisner, 1989). However, alteration in taste perception has received little attention regarding its impact on QOL and on the nutritional status of patients with advanced cancer. The effect of altered taste

perception on food intake and acceptance may impinge on the involvement in food related activities in a social context and this has not been fully investigated.

The following chapter will introduce taste perception and other symptoms associated with cachexia in patients with advanced cancer. Focusing on the causes of altered taste perception, the following sections examine the prevalence and causes of this symptom in a group of cancer patients receiving palliative care. Whilst patient may associate this with chemotherapy, there is evidence to suggest that alterations in taste perception occur in patients not receiving or who have never received any active treatment (Grosvenor *et al*, 1984). The exact mechanisms of altered taste perception in patients not receiving any treatment are unknown. Particular emphasis is given to the impact of this symptom on QOL and the nutritional status of patients with advanced cancer.

1.2 Cancer cachexia syndrome

In response to injury or trauma, a physiological protective mechanism response is triggered. Initially this local inflammatory response encompasses compensatory mechanisms such as the production of cytokines. In small quantities, cytokines serve to promote wound healing but chronic production of cytokines, such as in malignancy, results in an imbalance of homeostasis (Grimble 1996, Noguchi *et al*, 1996). With growing tumours, cytokines have systemic effects on host organs and may directly exacerbate cachexia (Cederholm *et al*, 1997).

Cachexia, derived from the Greek *Kakos* (bad) and *Hexis* (body habitus) is a common manifestation of neoplastic disease, characterised by a number of metabolic abnormalities, resulting in overt changes in body composition (Mercandante, 1996). Clinical manifestations of cachexia may be divided into two categories: 1) physical symptoms that include lean and fat tissue atrophy, anorexia, and lethargy, and 2) biochemical alterations such as anaemia, hypoalbuminaemia and glucose intolerance (Kern and Norton, 1988). The production of cytokines, mediators of the inflammatory response to neoplastic disease, has been implicated in the metabolic alterations associated with cachexia. This suggests that circulating cytokines produced in response to a tumour may cause a significant component of the weight loss. A closer insight into the pathophysiology of cancer weight loss and associated symptoms may therefore enhance the efficacy of specific treatments and may have a positive impact on QOL as well as other clinical outcomes.

1.2.1 Symptoms associated with cachexia

A loss of appetite is particularly apparent in malignant disease (DeWys, 1978; Cohn *et al*, 1981). The presence of pain, lack of sense of well-being, anxiety, and hospitalisation can all predispose to anorexia (Padilla, 1986). This is clearly illustrated in a study by Feuz and Rapin (1994) who noted that in over one hundred elderly patients with advanced cancer, dietary intake increased following successful pain control. The presence of anorexia is clearly illustrated in a study by Giacosa and colleagues (1996) who examined the dietary intake of 281 patients with cancer using food diaries completed for three days. Mean energy intake of this group was 1207 ± 372 s.d. kcal/day (17 ± 6 s.d.% protein, 38 ± 19 s.d % carbohydrate and 38 ± 16 s.d % fat). Patients who were weight losing had a lower energy intake than weight stable patients.

In a study by Grosvenor and colleagues in 1989, when energy intake was expressed in relation to body weight, no differences were noted between the weight losing patients (n 170, 31.4 ± 1.5 sem kcal/kg weight/day) compared to the weight stable patients (n 84, 30.5 ± 2.2 sem kcal / kg weight / day). Conversely, when energy intake was expressed relative to pre-illness body weight, weight losing patients consumed less energy (28.9 ± 1.2 sem kcal/ kg pre-illness weight/ day) than their weight stable counterparts (33.5 ± 2.2 sem kcal/ kg pre-illness weight/ day). Whilst this illustrates the presence of anorexia in weight losing cancer patients, the mechanism responsible for this component of cachexia in cancer patients remains poorly understood.

Many symptoms associated with advanced cancer and its palliative treatment contribute to a reduction in appetite (Trant *et al*, 1982; deConno *et al*, 1989, Mercandante, 1996). Grosvenor and colleagues (1989), examined symptoms associated with anorexia in 254 patients with a variety of unresectable tumours (n=93, colon n=50, prostate n=23, oropharyngeal n=18, breast n=15, gastrointestinal n=13 and others n=42) which included 39 patients who had received no previous chemotherapy or radiotherapy. Symptoms identified by multivariate analysis as occurring more frequently in patients with weight loss during their disease included early satiety, vomiting, dry mouth and the presence of taste changes.

1.2.2 Clinical impact of weight loss in cancer

Weight loss and reduced appetite are often the primary reason for patients seeking medical attention before diagnosis. Weight loss is one of the most frequent and serious problems confronting clinicians in the management of cancer (Theologides, 1972). Moreover, the size of the tumour does not appear to influence the amount of weight loss which suggests that circulating factors perhaps influence the overt weight loss (Tisdale, 1991). DeWys and colleagues in 1980 found that in a group of patients (28% malignant colorectal cancer and 14% breast cancer) had lost more than 5% of their usual body weight in a period of six months prior to diagnosis. Whilst these symptoms are troublesome and distressing for patients, clinical outcomes may be affected by significant amounts of weight loss (Fearon and Preston, 1990; Maltoni, 1995; *et al*, 1993).

The clinical impact and prognostic effect of severe weight loss have been studied extensively. A 40% loss of lean body mass is regarded as incompatible with life and it is estimated that up to 40% of all cancer patients die solely from malnutrition associated with the cachexia syndrome (Grant, 1990). Weight loss also leads to a loss of muscle mass contributing to reduced muscle strength and decreased mobility (Kern and Norton, 1988) which may also have psychological impact on QOL.

1.3. Mechanisms of cachexia

1.3.1 Altered metabolism in cancer weight loss

Although an inadequate energy intake is considered a major factor in contributing to weight loss in cachectic patients, the effect of altered energy expenditure undoubtedly plays a role. Studies in this area are conflicting, suggesting that cancer patients are either hypermetabolic, hypometabolic or have normal energy metabolism (Dempsey *et al*, 1983). Variations in energy expenditure may in part be due to biological differences as well as differences in the types of cancers studied, body composition (accounting for the amount of metabolically active lean body mass), stage of the disease and different methodologies used to measure energy expenditure. However, the consensus would appear to be that cancer patients have increased energy expenditure coupled with an ongoing inflammatory response (Kern and Norton, 1988; Keller, 1993a).

Staal-van den Brekel and colleagues (1995) noted that hypermetabolism and weight loss (>10% pre-illness weight loss) in patients with non-small cell lung cancer were associated with a systemic inflammatory response demonstrated by elevated levels of inflammatory cytokine mediators (Interleukin-1 β , Tumour Necrosis Factor α and Interleukin-6) and acute phase proteins such as C-Reactive Protein. Over 25 years ago, Theologides (1972) suggested that increased energy expenditure may be due to the growth of malignant tissue imposing greater energy expenditure than normal tissue. However, it is generally thought that the amount of tumour tissue present may be too small to account for the increased oxygen

consumption observed and that other factors are therefore involved (Kern and Norton, 1988).

Weight loss in cachexia differs from that of weight loss due to simple starvation. In the latter, there is relative sparing of lean tissue with preferential use of endogenous fat stores. In prolonged starvation, glycogen stores become depleted at about 36-72 hours following cessation of eating and the brain adapts to using ketone bodies, products of fatty acid breakdown, to supply glucose as an energy source. In response to the production of acute phase reactants associated with the cancer state, there is an accelerated mobilisation of host protein stores (Espat *et al*, 1994). Following nutrient deprivation in cancer, stores of glycogen and fat are broken down by glycolysis and lipolysis respectively to produce life-threatening skeletal muscle depletion (Lundholm *et al*, 1976). The full extent of weight loss may often go unrecognised due to an expansion of the extra-cellular water space (Heber and Tchenedyian, 1992) which masks any visual reduction in weight.

In cancer cachexia, derangements of metabolic pathways lead to abnormalities of host carbohydrate, protein and fat metabolism, despite adequate nutritional intake (Keller, 1993a). One reason why increased carbohydrate metabolism is a significant contributor to the redistribution and depletion of body protein muscle stores is the energy drain on the host due to increased hepatic gluconeogenesis (Kern and Norton, 1988). As previously described, cancer patients appear to exhibit an increased rate of proteolysis, a reduced ability to oxidise exogenous glucose, and an increased rate of lactate production. Lactate production, anaerobically oxidised is a more expensive energy producing cycle. Increased glucose and glycerol turnover rate could in part account for the increased oxygen consumption and energy

expenditure associated with weight loss in cancer cachexia. In addition, the tumour may have an effect on glucose metabolism in the liver (Burt *et al*, 1983). There also appears to be a maladaptive response resulting in fat mobilisation rather than fat storage. Alterations in fat metabolism, resulting in hyperlipidaemia and fat tissue loss may occur due to a defect in the enzyme activity of lipoprotein lipase, responsible for the clearance of lipids from blood. Weight losing cancer patients have demonstrated increased rates of glycerol and free fatty acid turnover compared with patients not exhibiting weight loss (Shaw, 1987).

1.3.2 Mediators of cachexia

Studies have focused on the identification of mediators that may be implicated in the tissue wasting of advanced cancer patients. A strategy to reverse or minimise the effects of such mediators may permit successful treatment modalities to improve symptom control and maximise QOL.

As part of the inflammatory response to the presence of a tumour growth, the host produces small molecular weight proteins called cytokines (Cooper *et al*, 1993), exhibiting a range of biological activities (Goh, 1990). Disease-induced changes in cytokine production result in several metabolic changes in cancer patients that can adversely affect nutritional status. Advances in molecular biology research in cancer indicate that cachexia weight loss may result from excess production of cytokines (Moldawer *et al*, 1992; Cangiano *et al*, 1996).

Cytokines are aptly described as mediators of defence and mediators of disease (Meydani and Dinarello, 1993). In defence, cytokines play an important role in normal T-cell response, tumour killing, non-specific resistance and anti-inflammatory processes. Changes designed to destroy the pathogen are characterised by fever, proteolysis in peripheral tissue and enhancement of the activity of the immune system (McNamara *et al*, 1992). In inflammation, cytokines significantly alter the metabolic processes of the liver, which responds by producing acute phase proteins, such as C-Reactive Protein (CRP; Banks *et al*, 1995). Cytokines act by mobilising nutrients from peripheral sites to provide nutrients for the synthesis of acute phase proteins (Kern and Norton, 1988) which are produced in preference to other plasma transport proteins such as albumin and transferrin (Falconer *et al*, 1995). When produced in large numbers, cytokines spill over into the circulation and act systemically. Persistent secretion results in depletion of host muscle mass and mobilisation of peripheral tissue, contributing to cachexia weight loss (Heber *et al*, 1992; Fong *et al*, 1989).

The effects of pro-inflammatory cytokines interleukin-1 β (IL-1 β), interleukin 6 (IL-6) and Tumour Necrosis Factor α (TNF α) in particular play important roles in the metabolic changes observed in cachexia (Kern and Norton, 1988, Moldawer *et al*, 1992). Following tissue damage, cytokines initiate a cascade of effects, which include an acute phase response, and the activation of inflammatory cells through secondary release of haemopoietic growth factors. The cascade illustrates a network of interactions whereby macrophages signal fibroblasts as well as immunocompetent T and B cells. Cytokines induce an acute phase response in the liver, which results in an alteration in hepatic protein synthesis and alteration in plasma protein composition.

Acute phase protein response

The presence of an acute phase protein response has been demonstrated as the most significant independent predictor of survival in patients with unresectable pancreatic cancer (Falconer *et al*, 1995). This group found that the mean survival of patients with an acute phase response (CRP>10mg/L) was reduced (66 days) when compared to patients not mounting this response (222 days). McMillan and colleagues in 1995 noted a higher recurrence of metastatic disease in colorectal cancer patients with an acute phase response (11 out of 15 patients) compared to those with no response (2 out of 21 patients). In a study by Gough and colleagues (1996), clinical outcomes were studied in a group of 13 patients with metastatic cancer and 7 healthy volunteers. These clinical outcomes included the acute phase response, TNF α production, phytohaemagglutinin response and survival status. The acute phase response, measured by an elevated CRP, correlated with survival ($r=0.69$, $p<0.05$) and albumin ($r=0.65$, $p<0.05$) only. TNF α did however, correlate with impaired lymphocyte function in patients ($r=0.56$, $p<0.05$) which suggested that impaired lymphocyte function may influence TNF α production and metabolic disturbances in cancer cachexia.

Based on *in vitro* studies, Banks and colleagues (1995) demonstrated that IL-1 β , IL-6 and TNF α are key mediators of the acute phase response. In animals treated with IL-6, the fastest response was observed for the acute phase proteins, CRP and amyloid A. IL-6 induced changes in the majority of the acute phase proteins *in vivo* but, as the authors suggest, TNF α and IL-1 β (which were not measured) may have also synergistically contributed to the effects observed with IL-6.

TNF α 'cachectin' has been suggested to be the central mediator of the metabolic response to the presence of a tumour (McCall *et al*, 1991; Gelin *et al*, 1991). TNF α stimulates the synthesis of acute phase response and induces IL-1 β release from endothelial cells and macrophages. The net effect of TNF α appears to encourage mobilisation of peripheral energy substrates required by the liver to meet the increasing demands of an activated host defence system (Tracey *et al*, 1989). The association between increased TNF α production and weight loss has been clearly demonstrated in a study of breast cancer patients (Knapp *et al*, 1991). Animal studies have demonstrated that TNF α production induces cachectic symptoms such as anorexia, weight loss, anaemia and depletion of whole-body proteins and lipids (Mahony and Tisdale, 1989). In one study, Llovera *et al* (1994) demonstrated that 4 days after the chronic administration of TNF α , increased circulating levels of urea concentrations and elevated urinary levels of 3-methylhistidine, an indicator of muscle protein catabolism were noted. Production of Prostaglandin PGE₂ was enhanced in response to chronic administration of TNF α , which suggested that the anorectic effect of TNF α may be mediated by a prostaglandin intermediate. Weight loss and reduced food intake appeared to be cytokine-dose related and occurred within the first 24 hours.

Interleukin - 1 β

Interleukin 1 β (IL-1 β), the predominant form of interleukin 1 series, is an important mediator of local and systemic responses in inflammation. In particular, IL-1 β plays a role in mediating the production of acute phase proteins perhaps as a result of the inability of IL-1 β to induce prostaglandin synthesis. The rate limiting step in prostaglandin synthesis is the release of fatty acids from membrane phospholipids, some of which undergo lipohydrogenation, which alters immune cell function (Dinerallo *et al*, 1990).

In a study by Opara and colleagues (1995), the amount of IL-1 β in cerebral spinal fluid collected in anorectic tumour-bearing rats and healthy controls was measured. Daily dietary intake was significantly lower in tumour-bearing animals as compared to controls (7.1 ± 1.1 g/day vs 12.0 ± 1.1 g/day, $p < 0.005$). Moreover, lower dietary intakes were coupled with an increased amounts of IL-1 β detected in cerebral spinal fluid. IL-1 β was detected in 8 out of 13 of the tumour-bearing animals compared to none of the healthy animals. Further animal work by this research group has shown that anorexia may be caused by an indirect increase in IL1 β production stimulated by hypothalamic serotonin activity. The ventromedial hypothalamus (VMH) appears to be the central site for the depressive effects on food intake of IL1 β . Subdiaphragmatic vagotomy attenuated the reduction in food-motivated behaviour of animals induced by IL-1 β (Watkins *et al*, 1995) which indicated that a peripheral neural signal may also be involved in the action of IL-1 β . Several other animal studies have examined the effects of IL-1 β to explore the exact mechanism of action of this cytokine. Laviano and colleagues (1995) suggested that cancer anorexia in an animal model involves the direct action

of IL-1 β on the VMH. The injection of a VMH IL-1 β antagonist correlated with an improvement in food intake. Further work by this group demonstrated that, following peripherally infused IL-1 β , food intake was reduced (Debonis *et al*, 1995). Earlier work in humans by Mrosovsky *et al* (1989) suggested that IL-1 β lowers a set point for body weight and key findings by Yang and Meguid (1995) suggest that IL-1 β induces anorexia centrally. Furthermore, in a study by Gelman and Klundholm (1992) blockade of prostaglandin 2 activity, a mediator of cytokine activity, resulted in attenuation of anorexia in rats. The role of IL-1 β in the alteration of neural signalling may have important implications in taste sensation that is controlled by similar signalling messages.

Other cytokines mediating changes in nutrient metabolism

Interleukin 1 cytokines are mediators in a broad spectrum of biological activities that includes the inflammatory response. Ling and colleagues (1996) demonstrated that acute and continuous infusion of IL-1 α for 6 days to rats, resulted in reduced food intake and weight loss. This was coupled with an increased production of the acute phase response, loss of muscle protein and reduced circulating plasma zinc levels. IL-1 α exerts a variety of physiological effects either alone or in combination with TNF α and IL-6. Oldenburg *et al* (1993) observed an association between IL-1 α receptor blockade and a reduced plasma IL-6 response, suggesting that the benefits achieved by IL-1 α blockade are mediated by reduced systemic IL6 production.

To summarise, the cytokines, $\text{TNF}\alpha$, $\text{IL-1}\beta$ and IL-6 appear to have a role in altering metabolic processes in cancer patients. More recent research demonstrated that the effects of the pro-inflammatory cytokines, often in combination, are mediated via the production of acute phase proteins and indirectly through modulation of neuronal activity. Due to the known metabolic and nutritional derangements that occur in the host mediated by $\text{TNF}\alpha$, $\text{IL-1}\beta$ and IL-6 , this study concentrates on these cytokines.

1.4 Nutritional management of cachexia syndrome

1.4.1 Use of novel substrates to manipulate cachexia

To minimise anorexia, the development of strategies that concentrate on correcting metabolic derangements, which may prevent effective utilisation of nutrients, is of prime importance. Our understanding of the effects of malnutrition on host immune defences is well known and provides the basis of the treatment of cancer. However, nutrition is only one of the many factors that modulate host defence mechanisms. The benefits of traditional aggressive nutritional support in providing adequate energy to meet anabolic demands have proved futile (Chlebowski *et al*, 1996). The focus of current research is the role of specific nutrients as regulators of the anticancer host defence mechanism and the control of nitrogen metabolism and tumour growth (Heys *et al*, 1996).

The amino acids arginine and glutamine, used as metabolic fuels in times of stress, have in particular received much attention. Diets supplemented with these amino acid have been shown to reduce post-operative morbidity in patients with cancer and to reduce bacterial translocation and improve nitrogen retention. Important effects on host defence such as increasing phagocytic activity in macrophages have been noted in patients supplemented with both amino acids (Barbul, 1986; Kirk and Barbul, 1990). In one particular study (Daly *et al*, 1992), patients with gastrointestinal cancer prior to surgery were randomised to either receive glutamine supplemented feed via jejunostomy or a standard jejunostomy feed. The supplemented feed provided more nitrogen (15.6g/day vs 9.0g/day) and these recipients were

less in negative nitrogen balance (-2.2g/day vs -6.6g/day, $p < 0.05$). Although the results are limited due to small number of patients, the supplemented diet group had significantly lower rates of pneumonia and wound complications. Animal studies appear to confirm this thought as oral glutamine supplementation may reduce tumour growth by enhancing natural killer cell activity (Fahr *et al*, 1994).

1.4.2. Fatty acid manipulation of cytokine action

In more recent years, the use of the ω -3 (omega 3) fatty acids has received much interest in nutritional support. Marine oils are a rich source of the fatty acids, eicosapentaenoic acid (EPA, 20:5 ω -3) and docosahexaenoic acid (DHA, 22:6 ω -3). High intakes of these polyunsaturated acids appear to have pharmacological properties including inhibition of anti-inflammatory, anti-thrombotic effects and altered lipoprotein metabolism. The incidence of many inflammatory diseases including coronary heart disease and psoriasis are lower in Eskimos who ingest diets rich in n-3 fatty acids compared with healthy European controls (Sanders, 1993). In relation to the anti-inflammatory effects of n-3 fatty acids, EPA has been implicated in the amelioration of the acute phase response. Few studies have investigated the effect of fatty acid supplementation on the acute phase response *in vivo*. Cooper and colleagues (1993) investigated the effects of diets of healthy 18-36 year old male and females supplemented with 4.5g fish oil daily for 6-8 weeks (1.15g EPA and 1.56g DHA / day). Following 6-8 weeks, fish oil supplementation was associated with a reduction of *in vitro* production of pro-inflammatory cytokines.

Previous work by Endres and colleagues (1989) measured *in vitro* stimulation of peripheral blood mononuclear cells following the addition of endotoxin as a stimulus for cytokine production. In healthy subjects who had supplemented their diet with 18g fish oil daily for 6 weeks, cytokine synthesis (IL1 β , IL1 α and TNF α) was suppressed ($p<0.05$). Moreover, a 62% cytokine reduction was noted 10 weeks after ingestion. More recently, Tisdale (1996) in experimental animal models demonstrated the effects of diets supplemented with fish oil. Most strikingly, host weight loss was inhibited by this intervention and occurred without an alteration in either total energy or nitrogen intake. EPA was found to directly inhibit tumour-induced lipolysis and protein degradation of skeletal muscle in cachexia. The authors postulated that this may be due to an inhibition of the rise in muscle prostaglandin E2 in response to EPA. This study demonstrated the properties of EPA, in altering the mechanism of action of tumour-produced catabolic factors. Billar and colleagues in 1988 observed a significant decrease in the *in vitro* IL-1 β production by Kupffer cells in an animal diet containing 15% energy as fish oil for 6 weeks as compared to diets containing 15% energy as corn oil. More recently, Kenler and colleagues (1996) examined the outcomes of fish oil supplemented jejunal feeding. In a group of post-operative gastrointestinal cancer patients, a reduction in gastrointestinal complications and infections were noted in patients receiving an omega 3 fatty acid enriched jejunal formula compared to patients receiving an iso-nitrogenous jejunal feed. This finding was coupled with a significant incorporation of EPA into the plasma and erythrocyte phospholipids and modulation of urinary prostaglandin levels.

Encouraging results from animal studies have paved the way for human studies. For example Endres and colleagues (1989) measured IL-1 β and TNF α production by peripheral blood

mononuclear cells in diets supplemented with 2.7g EPA and 1.85g DHA daily. IL1 β production was significantly reduced after 6 weeks supplementation where stimulated cells produced a 42% reduction in IL1 β (4.2 ng/ml) from pre-supplementation level (7.4 ng/ml IL1 β ; $p<0.005$). Ten weeks following supplementation, IL1 β production further decreased by 60% (2.9ng/ml, $p<0.005$) and returned to pre-supplementation levels 20 weeks after cessation of supplementation. Changes in IL1 α and TNF α were similar to that demonstrated by IL-1 β . Meydani and colleagues (1991) investigated age differences in the effects of ω -3 fatty acids. Six young women (23-33 years) and 6 older women (51-68 years) were given 2.4g/day ω -3 fatty acid for a period of 3 months. Supplementation with ω -3 fatty acids reduced IL-1 β synthesis two-fold in the younger group and 10 fold in older group ($p<0.05$). In addition, TNF α was reduced by 58% and 70% in the younger and older ($p<0.05$) groups respectively and IL6 was reduced by 30% and 60% in the younger and older groups respectively ($p<0.05$). Reduction of cytokine levels associated with an anti-inflammatory effect, appeared more dramatic in the older group compared to younger group.

In patients with unresectable carcinoma of the pancreas, Wigmore and colleagues (1995) demonstrated beneficial effects following daily supplementation of 12g fish oil (18% w/w EPA). Weight loss was reversed or halted accompanied by a significant decrease in the acute phase response (CRP) in the EPA supplemented group. All patients at baseline were losing weight (mean weight loss=2.9kg/month). However, the mean post supplementation weight gain of 0.3kg was significantly different from baseline measurements ($p<0.005$). Eleven out of eighteen patients had gained weight, whereas three patients remained stable and four continued to lose weight but at a reduced rate. There was no difference in upper arm

anthropometric measurements and energy expenditure (measured by indirect calorimetry) after the supplementation period. Coupled with these weight changes, the concentration of EPA in plasma phospholipids increased from the pre-supplementation level to a median of 5.3% of total fatty acids following supplementation. This was paralleled with a reduction in arachidonic acid from 13.2% of total fatty acid pre-supplementation to 7.1% post supplementation. Dose escalation studies using high purity EPA in 22 pancreatic cancer patients showed a reduction in the rate of weight loss in the majority of patients (Wigmore *et al*, 1996). Isolation of EPA indicated that this omega 3 fatty acid was responsible for the attenuation of weight loss. Purasir *et al* (1994) examined the effects of EPA and DHA supplementation (4.8g/day) on cytokines IL-1 β , IL-6 and TNF α in colorectal cancer patients. For the first 2 months, no significant changes in plasma cytokine production were noted. However, after 6 months, IL1 β production was reduced by 61%, IL6 by 86% and TNF α by 73%. Three months following cessation of supplementation (wash-out period), plasma levels returned to normal.

The use of EPA supplementation in weight-losing patients is not unique to malignancy states. Diets of weight-losing patients with autoimmune deficiency syndrome (mean weight loss during illness 13.7kg) supplemented with 18g fish oil supplements (18% w/w EPA) did not result in changes in weight after a 10 week supplementation period (Hellerstein *et al*, 1996). In addition, no change in dietary intake throughout the supplementation period was noted. These patients were already immuno-compromised due to their HIV infection and therefore the mechanism in cancer patients may not be the same.

Many of these studies have demonstrated that EPA has the potential to down-regulate the acute phase response in patients with cancer and that it is likely to involve suppression of the cytokines mediating this response. This correction of the pathological mechanism responsible for anorexia remains the goal of treatment for cancer anorexia.

1.4.3. Mechanism of the manipulation of cytokine action by fatty acids

Fatty acids have important structural roles in cells and also act as precursors for numerous bioactive metabolites such as eicosanoids. Eicosanoids such as leukotrienes, prostaglandins and thromboxanes have been implicated as contributing to the development of inflammatory and atherosclerotic disease. The presence of omega 3 fatty acids leads to a change in the profile of prostaglandins and leukotrienes produced during stress and sepsis. Many studies have suggested that dietary fats influence eicosanoid and prostaglandin metabolism, following incorporation of eicosapentanoic acid (20:5, ω -3) into membrane phospholipids. Prostaglandins appear to modulate the production of cytokines that play a role in the mediation of fever and the associated increase in energy expenditure.

Arachidonic acid is a main component of membrane phospholipids and a precursor in mammalian cells in the production of prostaglandin 2 series synthesis via the cyclooxygenase pathway (Dinarello *et al* 1990). More recently, Caughey and colleagues (1996) investigated the mechanism of action involving eicosanoid mediators. Prostaglandin E₂ (PGE₂) production has been shown to be inhibited by fish oils. This process is important as it has been shown that one mechanism by which IL-1 β induces anorexia appears to require cyclooxygenase

metabolites, such as PGE₂. EPA (20:5 ω -3) also acts as a substrate for eicosanoid production and yields prostaglandins of the 3 series, which have lower biological activity which compete for binding sites that can reduce the production of arachidonic acid (Willis, 1981; Meuller and Talbert, 1988). The supply of fatty acids for eicosanoid synthesis is directly related to fatty acid composition of membrane phospholipids and influenced by dietary fat intake (Willis, 1981).

Arachidonic acid metabolism is known to mediate the biological activity of IL-1 β in lymphocyte, neutrophils and muscle cells (Hellerstein *et al*, 1989). Studies have shown that dietary ω -3 fatty acid modify the endogenous eicosanoid synthesis by competitive inhibition of arachidonic ω -6 fatty acid uptake into cell membranes (Meydani and Dinarello, 1993). This involves competition with arachidonic acid, a precursor for eicosanoid synthesis, as a substrate for the cyclo-oxygenase enzymes. In addition, ω -3 fatty acids may reduce cytokine induced expression of endothelial leucocytes and reduce secretion of mediators of inflammation (de Caterina *et al*, 1994; Meuller and Talbert, 1988).

The main effects of EPA include reduced formation of arachidonic acid metabolites of the prostaglandin 2 series, modification of the activity of cyclooxygenase and lipoxygenase and therefore the nature and the biological activity of the eicosanoids formed by these enzymes.

1.5. Outcomes of nutritional management in advanced cancer

1.5.1 Clinical outcomes of nutritional support

The use of nutritional support in preventing or controlling the symptoms of cachexia has received much attention in recent years. The difficulty in defining efficacy is in identifying appropriate outcomes. A study by Daly and colleagues (1986) failed to demonstrate any improved outcomes with the use of aggressive nutritional support in patients following general surgery. This suggested that despite improving intake, derangements in nutrient metabolism persist uncorrected. Nutritional support (both enteral and parenteral) may not always be effective in improving the nutritional status of undernourished cancer patients due to continuous changes in host metabolism (Laviano and Meguid, 1996). Aggressive nutritional support may only in the short term, improve nutritional status, increase tolerance to therapy and improve response to non-operative treatment (Detsky *et al*, 1987; Torosian and Daly, 1986).

Many ethical issues surround the use of nutritional support in patients with advanced cancer (Dunlop *et al*, 1995 Taylor *et al*, 1989). A multi-centered study, involving experienced nursing staff examined the concepts involved in the decision to provide aggressive nutritional support to patients with advanced terminal cancer (Davidson *et al*, 1990). A dilemma in the ethical justifications regarding the use of nutritional support in palliative care focused on the uncertain benefits of nutritional support in terms of survival and QOL in patients with terminal disease.

Traditionally, objective indices of the outcomes of cancer treatment and the relief of symptoms have focused on tumour response and survival, whereas hospice care focuses on patients QOL. The World Health Organisation's definition of QOL is 'a state of complete physical, mental and social well-being and not merely the absence of disease and infirmity'. Similarly Twycross (1987) eloquently described a good QOL to exist when "the hopes of an individual are matched and fulfilled by experience". This subjective parameter may alter over time due to perceptions of the impact of the disease and circumstances (Calman, 1984; Schipper, 1992).

The benefits of nutritional support for end-stage cancer patients may not be simply improving nutritional status but may provide benefits in terms of QOL (Shike, 1996; Ottery, 1995). Overt changes in nutritional status which occur within this patient group may have a considerable effect on QOL of patients. In a study of over 120 cancer patients by Padilla and colleagues in 1983, a good appetite and the physical ability to eat were important factors contributing to the patients QOL. In a more recent review of health-related QOL assessment tools, Padilla (1992) highlighted symptoms such as the ability to eat, appetite, a concern for weight changes and the pleasurable aspect of eating such as taste perception as key dimensions of QOL. However, Kaasa (1992) reiterates that the importance of each dimension may differ between many individual factors dependent on treatment, age and stage of disease.

Quality of life assessments are important clinical outcomes of treatments, assessing the balance between possible risks, burdens and benefits of any treatment regimens (Gough *et al*, 1983). One such example of clinical research was in the use of an anabolic steroid that has a

stimulating effect on appetite, *megesterol acetate* but, no improvement in QOL was observed, despite increase in appetite (Chlebowski *et al*, 1996). This suggested that objectively measured changes of increased appetite did not influence any QOL parameters. Beck and Tisdale (1990) demonstrated that *megesterol acetate* was effective in preventing weight loss and improving appetite in patients with a good dietary intake.

A unique study by Larsson and colleagues (1995) explored the relationship between undernutrition and QOL, hypothesising that malnutrition was associated with a lower QOL. In almost 200 patients including those with malignancy, under-nutrition was identified when the criteria for 3 or more parameters of undernutrition were met (% recent weight loss, triceps skinfold thickness, arm muscle circumference, pre-albumin and albumin). In this study by Larsson, an assessment of QOL was made based on a tool developed and tailored for this study population. Thirty nine per cent of patients with malignancy identified as under-nourished showed significant impairment in many of the domains of QOL studied. In particular, weight loss >10% and low pre-albumin were associated with deteriorated well-being. This study has important implications for end-stage cancer patients, demonstrating a relationship between nutritional status and QOL.

1.5.2 Nutritional assessment

Patients with advanced cancer are often elderly, under-nourished with multi-system failure. These patients are characterised by a dynamic state in which the nature and intensity of symptoms and response to treatment are continuously changing. An assessment of nutritional

status may be used to assess the impact of symptoms of cachexia on the nutritional status of patients with cancer and subsequently the impact of any nutritional intervention. Shike and Brennan (1989) outlined the importance of nutritional assessment supplementing the information regarding symptoms obtained in a medical history. The effects of disease symptoms on mood, function and other QOL dimensions are essential for studies in the palliative care setting (Donnelly and Walsh, 1996).

Two main components of the nutritional assessment of patients include determining body composition and dietary intake. Within clinical research, an accurate objective assessment and appropriate interpretation of data is required to detect significant changes in the nutritional status of patients.

Body weight comprises of lean body mass (LBM) consisting of actively-metabolising tissues of the body but excluding extra-cellular protein; fat mass (FM), comprising subcutaneous but not cellular lipo-protein; and total body water with intra and extra-cellular components (Lohman, 1981; Heymsfield *et al*, 1989). FM has been demonstrated to account for the majority of weight loss seen in cancer patients (Cohn *et al*, 1981). However, in an advanced stage of malignancy, loss of LBM has also been demonstrated. Body cell mass (BCM) represents the total mass of all the cellular elements in the body and therefore the metabolically active component of the body (Moore *et al*, 1963). It is an index of metabolic activity including oxygen consumption, carbon dioxide production, energy and protein requirements. Water balance can fluctuate due to an increased production of acute phase proteins in preference to albumin, resulting in reduced albumin levels.

Although, nutritional assessment provides an objective insight into nutritional status of cancer patients, many of the reference tools of assessment have practical and theoretical limitations for use in this population (Bistrian, 1986; MacFie and Burkinshaw, 1987). Body composition determination relies on accurate observer techniques and the use of appropriate tools within particular patient settings. Errors due to this measurement may be propagated in subsequent calculations of body composition and contribute to differences in the predictive value of this assessment (Fuller *et al*, 1991). However, Reilly and colleagues (1993) suggest that the errors incurred with each choice of method have little impact when making comparison within a group.

Reference techniques for the assessment of body composition include isotopes, body density, total body potassium and dual energy X-ray absorptiometry. However, the use of these procedures are often limited due to the time taken to complete the assessment, availability of equipment, specialist knowledge for operation and non-portable equipment. Whole body density involves weighing the patient when fully submerged in water (Jebb and Elia, 1993) and is therefore not a technique suitable for the assessment in immobile subjects or even in terminally ill patients. Total body potassium is performed in a whole body counter of which only a few centres of research have such equipment. The measurement usually takes more than one hour to perform and for practical purposes, as it requires patients to remain still for a period of time, is therefore not suitable for terminally ill patients.

1.5.3. Bedside techniques for measurements of nutritional status in patients with advanced cancer

The assessment of body composition in patients with advanced cancer requires non-invasive, bedside techniques. Some of the most commonly used 'bedside' techniques for nutritional assessment will now be discussed in relation to their use in the hospice setting and validation against the reference techniques.

Body weight

Weight assessment is often limited in non-ambulatory patients and in patients with advanced cancer where acute fluid balance changes may influence the interpretation of data. Body weight may be compared with 'ideal' sex and age specific weight tables (Lehmann *et al* 1991) or compared with 'ideal' weight for height tables (Metropolitan Life Insurance Tables). However, methods of expressing body weight often fail to consider the importance of pre-illness weight loss, a useful marker of changes in protein energy status. Weight loss reported by patients is a more useful indicator of changes in body composition and hence reflective of nutritional status.

Body Mass Index

The measurement of height when used in relation to weight, is a useful indicator of body mass index (BMI) widely used in the clinical setting as a frame of reference. BMI (mass in kg divided by height in meters squared) is the most commonly used ratio in younger adults. However, it is not an appropriate measure in the elderly as it does not take account of age-associated changes in height or stature. Sex specific indices, demiquet (mass kg / demispan m^2) and mindex (mass kg / demispan m) have been developed using the assessment of demispan.

Triceps Skinfold Thickness

Approximately 50% of body fat is located subcutaneously (Lukaski, 1987). Skinfold measurements provide an indication of the size of the subcutaneous fat layer and are of great clinical use in the estimation of energy reserves. Skinfold thickness measurements can be taken at one or more sites (triceps, biceps, subscapular and suprailiac) and the sum used to derive total endogenous fat reserves (Durnin and Wormseley, 1974). Two principle assumptions are made relating to the use of skinfold thickness: 1) the subcutaneous fat is proportional to total body fat and 2) the chosen site is representative of the average skinfold thickness across the surface of the whole body (Gurney and Jelliffe, 1973). Due to other fat deposits in the body such as inter-muscular, intra-muscular, surrounding the major organs and lipids in bone marrow there is considerable chance for biological variation in the relationship of measures of subcutaneous fat with total endogenous fat stores (Lohman, 1981). However,

in view of the errors and limitations in the assessment of fat mass, there are considerable merits in comparing skinfold data against reference percentiles (Norgan, 1991). However, in an elderly group with reduced mobility, the use of triceps skinfold thickness (TSF) measurement alone may be more appropriate. The triceps site is more accessible and less prone to the influence of oedema compared to the other sites. Measurements may then be compared with standard age and sex specific reference values, which are based on data from an assessment of 1600 healthy elderly subjects (Burr and Philips, 1983).

The use of TSF as part of nutritional assessment provides a simple, quick, cheap, readily available and non-invasive method of estimating the body's fat reserve. In a study by Fuller and colleagues in 1992, 28 healthy adults (BMI 20-28 kg/m²) were assessed using the reference techniques, Dual Energy X-Ray Absorptiometry, deuterium dilution and potassium counting and also the bed-side techniques namely skinfold thickness, impedance analysis (BIA), BMI and near infra red interactance. TSF was found to be as good a predictor of fat mass as the reference techniques in a group of subjects.

Errors in the measurement of TSF have been acknowledged in previous studies (Hall *et al*, 1980, Harris *et al* 1984). It is estimated that errors occur with either skinfold thickness greater than 15 mm or less than 5 mm which may arise due to difficulty differentiating between muscle and fat compartments in the mid-arm. Walker and Kindlen (1988) repeated TSF measurements on 5 occasions in 18 subjects by a trained and untrained observer and found significant error in estimating body fat by skinfolds thickness introduced by an inexperienced observer. However, the authors suggested that this error may be reduced by a relatively short

period of practice highlighted the importance of consistency in measurements by a single trained observer. Fuller *et al* (1991) examined inter-observer variation using a variety of bedside tools by 6 observers in 12 healthy adults. Variation as expected was greatest for skinfold measurements in assessing % body fat at 4 sites (coefficient of variation 11-18% individual skinfolds, 9% sum of 4 sites) and lowest for the measurement of weight (0.01% digital scales, 0.05% beam balance scales).

Arm Muscle Circumference

Mid upper arm circumference and subtraction of TSF may be used to estimate arm muscle circumference (AMC), an indicator of muscle mass and hence protein malnutrition. AMC is an index of skeletal muscle mass, which accounts for approximately 30% of the LBM, a useful tool in assessing protein mass. Furthermore, an assessment of arm muscle area (AMA) may then be made from arm muscle circumference.

Upper arm anthropometry assessments (AMC, AMA and TSF) make two main assumptions: 1) the upper arm is cylindrical, which ignores the contribution made by the humerus and 2) the symmetrical distribution of fat around the arm is a constant fraction of bone to muscle area (Heymsfield *et al*, 1982). Appropriate bedside tools may be used to identify under-nutrition. Guidelines suggested by Bistrian (1980) may be adopted to define Protein-Calorie Malnutrition, that is upper arm anthropometry < 5th percentile of reference data or less than 80% of mean standard reference value. Age and sex specific reference values exist for AMC and AMA data (Burr and Philips, 1983).

Hand Grip Dynanometry

Chronic under-nutrition associated with end-stage malignancy contributes to muscle fatigue and weakness. Skeletal muscle function, assessed by grip strength has been shown to be a useful indicator of muscle function and hence malnutrition (Kildjian *et al*, 1980; Webb *et al*, 1989). In a study by Phillips (1986) a low grip strength identified a population nutritionally 'at risk', correlating under-nutrition with muscle weakness. Kalfarentoz *et al* (1989) described hand grip dynanometry as a useful and inexpensive test which when compared against a subjective prognostic nutritional index, hence reflected reduced muscle strength in undernourished patients with gastro-intestinal cancer. Webb and colleagues (1989) have devised age and sex specific reference data for hand grip dynanometry.

Bioelectrical Impedance Analysis

Bioelectrical impedance analysis (BIA) measures the passage of a small alternating electric current (800 μ A) through extra-cellular water, measuring body resistance and impedance. Fat tissue is anhydrous and therefore all body water and fluids are bound in the fat free mass. Intra and extra cellular fluids behave as electrical conductors and cell membranes act as imperfect reactive elements (Foster and Lukaski, 1996). Body fluids and electrolytes are responsible for electrical conductance and cell membranes are involved in capacitance. A hydration fraction is used to calculate lean body mass and fat mass calculated by the difference from body weight. Population specific equations may be used to determine body composition (Roubenhoff, 1991).

There is limited published data on the use of BIA measurement in the management of patients with advanced cancer, including those with pronounced cachexia symptoms (Fredix, 1989). Gray (1988) found that BIA accurately reflected changes in total body water during normal starvation. In a recent study by Simons and colleagues (1995), 41 patients with advanced cancer, mainly primary lung diagnosis, underwent nutritional assessment including fat mass estimation by BIA and total body water determination by deuterium dilution. BIA was shown to have a predictive role in the assessment of nutritional status when compared to the reference method, deuterium dilution technique.

Jacobs (1996) highlights a major problem in the assessment of changes in lean tissue or the distribution of body water in severely ill patients. There is no accurate way to separate these changes from those solely due to alterations in hydration state. The inability of BIA to detect changes in body composition due to altered hydration states and to accurately assess the distribution of water between intracellular and extra-cellular compartment, limits its clinical use in starvation (Birmingham *et al*, 1996). In many patients with cancer, oedema is a significant confounding variable resulting from the malignancy, hypoalbuminaemia, and even lymphoedema (Kushner, 1992). Any changes in fluid retention may lead to inaccurate body composition determination, as the arm and leg contribute to approximately 90% of total impedance and therefore reflect whole body changes (Deurenberg *et al*, 1989). However, BIA is a viable technique for comparing group means in a population survey (Coward *et al*, 1988). In addition to anthropometry, BIA has an important role when more invasive methods are not practical (Guo *et al*, 1996).

In addition to anthropometry, BIA has an important role when more invasive methods are not practical (Guo *et al*, 1996).

1.5.4 Biochemical indices of nutritional status

Nutritional status may also be assessed using the measurement of hepatic protein synthesis but only if there is no ongoing inflammatory response. Albumin, a plasma protein with a half life of approximately 12 days is often inappropriately used as a nutritional indicator. Low albumin concentrations often noted in advanced cancer patients may not accurately reflect protein status but may be an index of 'illness'. This may be due to the expansion of the body cell mass and the subsequent dilution effect of serum albumin.

It is perhaps more appropriate to consider albumin in conjunction with an acute phase protein such as C-Reactive Protein (CRP). Elevated serum CRP (>10mg/L) coupled with low serum albumin (<30g/L) reflects the 'illness' of the patient rather than the nutritional state, whereas normal CRP coupled with low serum albumin is reflective of protein depletion.

1.5.5. Assessment of dietary intake

Another component of nutritional assessment is the determination of dietary intake. The measurement of the habitual intake of food is said to be one of the most difficult tasks to be undertaken in nutrition research (Acheson *et al* 1980). Problems include both the determination of dietary intake and the conversion of this information to nutrient value. There are two main techniques to estimate dietary intake: 1) recall of food consumed and 2)

measurement or recording of food eaten. Both methods are discussed in this section with reference to their practical use and validity within palliative care.

The 24-hour recall method is a simple and straightforward method relying on patient's ability to recall the exact intake in the previous 24 hours. However, a single day may not be representative of dietary intake due to daily variations. This is particularly evident with patients suffering from advanced cancer whose daily intake is influenced by a myriad of symptoms associated with a changeable disease process. The seven day recall method, providing a more representative estimate of dietary intake, may be an inaccurate method due to the reliance of memory over a 7 day period (Block and Hartman, 1989).

The recording of intake by weighing, measuring or estimating portion sizes may provide a reasonably accurate measurement of dietary intake. Bingham (1991) found a significant difference between the measurement of the food intake by estimating the weight of food portions and measuring the portion sizes. Patients frequently under- or over- report creating a biased result. In the clinical setting, these errors were overcome by weighing food items. To estimate food intake, this time-consuming method involves weighing food presented to the patient and thereafter weighing any uneaten food. Intake may then be converted into actual nutrient intake by the use of a dietary analysis package or dietary analysis food tables (McCance and Widdowson, 1992). Measurement by the investigator removes the emphasis on the quantity of food eaten by the patient and may also reduce any patient anxiety that would influence consumption. These are indeed important considerations in patients with advanced cancer when there is a requirement for sensitive and unobtrusive techniques.

The weighing technique has previously been adopted by researchers to assess the dietary intake of patients with advanced cancer and appears to be the most non-invasive and appropriate means of assessing intake. Walsh and colleagues (1983) used a partially individualised weighed technique. For five consecutive days, food offered to patients in the hospice setting was weighed when served. Individual plate wastage was subtracted from this original plate weight to give an estimated individual intake. However, foods provided by visitors were not included in the assessment of daily dietary intake.

Bingham and colleagues (1994) assessed the accuracy of seven methods of dietary assessment, namely, a simple 24 hour recall, a structured 24 hour recall method using photographs of portion sizes, two food frequency questionnaires, a seven day estimated record, a structured food frequency record and a structured food frequency record containing photographs of portion sizes. Dietary intake, measured by a four day diary method, was correlated with weighed records (Bingham, 1991).

Corli and colleagues (1992) devised a simple and easily acceptable tool used by patients to quantify daily calorie intake as compared to normal intake. Six key words were used to refer to different levels of food intake on a category scale. The patient assessed their dietary intake as one of these five categories: 'no intake', 'very little intake', 'normal', 'a lot' and 'maximum' intake. 'Normal' referred to the same amount usually eaten before illness, whereas 'a lot' referred to intake superior to the norm. Developed from a scale used by

patients to assess their pain intensity, this scale could be further adapted to assess the intensity of other nutritional related symptoms such as appetite, dry mouth and even taste perception.

1.5.6 QOL and nutritional status in advanced cancer

Despite the well-documented need to measure QOL in palliative care, it is a parameter that is indeed difficult to define and measure. An assessment instrument must take into account aspects of life and lifestyle that are important to individuals and measure the gap between experiences and expectations. Many assessment tools take into consideration key domains of QOL namely, physical symptoms, psychological distress, cognitive function, body image and sexual function (Cella, 1994).

QOL assessment tools need to be short so as not to burden the patient who may tire easily and also to maintain compliance. It has been recommended by Finlay and Dunlop (1994) that questionnaires should take no longer than 15 minutes to complete. Most authors now accept that the best source of information should be directly from the patient in order to eliminate observer bias. There is a very real danger that others may impose their own perception of anxieties into their assessment of the patient. In addition, it is important that the procedure for conducting research that it does not impinge on the patients QOL. There is a need to conduct the questionnaire sensitively within a supportive environment (Finlay and Dunlop, 1994).

An assessment of QOL may encompass the impact of symptoms such as alteration in taste perception and weight loss. In palliative care, there appears to be no reference tool for measuring QOL. Reliability (the ability to measure accurately and consistently what it is

meant to measure) and validity (the extent to which a tool measures what it purports to measure) are important considerations when choosing an assessment tool. More importantly, an assessment tool needs to examine questions relevant to the purpose of the test to provide a comprehensive coverage of the important constructs of interest that have been made. Several widely used tools in the clinical setting will be discussed with reference to their suitability for this particular study.

Global assessment of QOL

Firstly, a global measurement such as “How do you rate your feeling of well-being to-day?” may be recorded on a visual analogue scale. However, this rating does not give any indication about the relative contributions of the components of QOL. General measures of QOL may not be specific enough to capture small but significant changes in health status or levels of disease severity. This approach is more popular as it is multifactorial, individual, and dynamic. Donnelly and Walsh (1996) suggest that objectives of assessment of cancer patients may differ as the disease progresses, rendering it difficult to combine all domains into one QOL instrument.

The recently developed SEIQoL (Schedule for the evaluation of individual QOL) is an example of a global assessment of QOL (O’Boyle and Waldron, 1997). It measures three areas of QOL: 1) areas of importance highlighted by the patient, 2) how they currently regard their QOL in each of these areas and 3) what the relative importance of each of these areas for overall QOL. The clearest advantage of such a tool is that it incorporates the unique

perspective of the individual patients, therefore, focusing on issues that are pertinent to the patients own QOL.

Multi-dimensional assessment of QOL

Multidimensional assessment tools have been widely used within oncology (Spitzer *et al*, 1981). This index measures five areas, including physical activity, aspects of daily living, perception of own health, support from family and friends and outlook on life. A main advantage is the simplicity of the tool, which is quick to complete, and has been designed to be used by physicians to assess patients QOL. However, poor agreement between the patient and physician assessments have been reported using this tool (Slevin *et al*, 1988), highlighting the increasing importance of patient rather than doctor ratings. Maguire and Selby (1989) report that concentrating on five aspects of life reflects an over-reliance on the correlation between the different items that are components of each item. However, the Spitzer QOL tool has not been widely used in patients with advanced cancer.

The Rotterdam Symptom checklist, measuring the impact that treatment for cancer has on psychosocial functioning (Dettaes *et al*, 1988) is derived from items contained in several existing questionnaires. It contains 38 items each on a 4 point scale and asks respondents how much they have experienced particular symptoms over the last week. Although this questionnaire is lengthy to use, it has shown to have high reliability and validity against independent interviews.

Visual analogue scales

Visual analogue scales (VAS) have widely been used to rate subjective feelings and are useful when repeated tests are required. However, idiosyncratic interpretations of end phrases may reduce the clinical significance of individual scores (Maguire and Selby, 1989). Padilla and colleagues (1983) developed a tool to assess QOL in patients with cancer. This consists of a 14 item set of linear visual analogue scales, which specifically examine the patient's general physical condition, normal activities and personal attitudes regarding their QOL. The tool distinguished differences in QOL between healthy volunteers and patient with cancer that included those who were undergoing radiotherapy. Other linear analogue scales have been designed by Priestman and Baum (1976) and are increasingly being applied to palliative care.

Psychosocial Measures

The Hospital Anxiety and Depression Scale (HAD Scale, Zigmund and Snaith, 1983) is a validated tool consisting of 14 items which rate individual responses on a 4 point scale. Of these 14 items, 7 are concerned with anxiety and 7 with depression. It is designed to be completed by patients is quick to use and has proved useful as a screening instrument in the clinical setting (Girling *et al*, 1994). More recently, Hammerlid and colleagues (1997) found that, in a longitudinal study of patients with head and neck cancer receiving active treatment, the use of the HAD scale was sensitive to changes in symptoms during the study year. In this

study, symptoms such as swallowing problems, dry mouth and taste changes that increased over the treatment period, were associated with increasing psychological distress.

A literature search of assessment tools used in this area has failed to reveal a wholly satisfactory tool for the purposes of this current study. The main limitations are the length of completion and the amount of irrelevant data that would be unnecessarily collected. For this current study, a tool needed to be adapted to suit the aim of the research, that is, the assessment of QOL in relation to the impact of taste changes. Therefore, the main objectives of the tool adapted from the HAD scale was that it would reflect issues that were clinically relevant, satisfy research issues, and was practical to implement to provide a standardised assessment.

1.6. Altered taste perception associated with advanced cancer

1.6.1 Altered taste perception and QOL

Gustatory and olfactory perceptions play important roles in the determination of food selection and dietary intake and subsequent enjoyment of food (Drewnowski, 1997). The presence of taste aberrations in cancer cachexia has been cited as a factor contributing to cancer anorexia (DeWys 1978, Grosvenor *et al*, 1989; Duffy and Ferris, 1989). There is little information regarding the impact of changes in taste perception on dietary habits and nutritional status despite the indications that it may affect food intake and may have a significant effect on a patient's already poor nutritional status. An alteration in this function may disproportionately affect QOL and the ability to cope with changes in taste perception may therefore contribute to psychological and social well-being.

Harrison and colleagues (1997) examined the impact of radiotherapy and associated symptoms such as altered taste perception, swallowing difficulties and pain on the QOL of 36 patients with cancer of the tongue. Using functional and performance scales, QOL was altered by the impact of treatment or symptoms highlighted. Although the prevalence of oral problems may be greater in patients with cancer of the tongue who had received radiotherapy, the importance of taste changes in QOL is indicated.

1.6.2 Taste perception in patients with advanced cancer

One of the first nutritional studies in the hospice setting used a structured questionnaire to assess the prevalence of subjective changes in weight, appetite, taste perception and food preference (Walsh *et al*, 1982). Four fifths of patients (20 out of 25 patients) experienced weight loss, 17 reported anorexia and an alteration in taste perception was prevalent in approximately half of the patients (n=13). Of these 13 patients, five reported a general loss of taste, and the others more specific changes in taste acuity such as increased ability to perceive bitter and sweet tastes. As a consequence of taste alterations, seven patients were found to have an aversion to sweet foods and six had an aversion to meat and similar products. Changes in taste acuity were not related to any gastrointestinal symptoms, the length of illness or survival. In a recent review of oral problems Krishnasamy (1995) reported that in almost 200 cancer patients receiving palliative care, 77% were experiencing xerostomia, 37% taste alterations and 33% were experiencing other problems such as swallowing difficulties and soreness of the mouth. The prevalence of such symptoms is similar to findings of Aldred and colleagues (1991) who, from subjective information, found that, 26% of a heterogeneous hospice patient group (n 20) reported taste disturbances. Poor dental health and oral *Candidiasis* were noted as factors that may exacerbate poor taste perception by creating a physical barrier to taste bud stimulation.

Taste changes occurring in patients with cancer may result from both the disease process and therapeutic regimens (Mossman and Henkin, 1978; Holmes, 1993). With respect to treatment side-effects, changes in taste sensitivity may be attributable to cell death and to the damage to

microvilli of taste cells (Conger, 1973). Chemotherapy regimens act by utilising chemicals that interfere with mitotic activity and therefore destroy proliferating cells such as those of the taste buds. This was further highlighted by Beidler and Smith (1991) who demonstrated that the mitotic inhibitor vinblastin sulphate reduced dietary intake in an animal study. Holes (1993) found that in 72 patients undergoing cancer chemotherapy, 82% attributed the avoidance of one or more foods such as coffee, tea, citrus fruit, chocolate and red meat to taste aberrations. In this study, no relationship existed between food avoidance and primary tumour types. Cruikshank and colleagues (1989) noted that, in a group of head and neck cancer patients receiving radiotherapy, (n=74), 80% reported oral problems that included a dry mouth and altered taste perception which was associated with weight loss in this group of patients.

Over twenty years ago, the prevalence and magnitude of taste aberrations in cancer patients was first investigated. DeWys (1974) found that half of a group of 50 heterogeneous patients, reported a reduction in the pleasurable aspect of taste. The presence of other cancer-related symptoms such as weight loss, early satiety and the feeling of fullness were recorded by a semi-structured interview and were positively correlated with alterations in taste perception. In addition, the extent of disease was classified and patients with farther advanced disease more frequently reported taste alterations. Taste changes were reflected in food items that patients had consequently avoided which included meat products (32% patients). Taste perceptions for the four primary tastes (sweet, sour, salt and bitter) were objectively measured using the forced-choice technique described by Henkin and colleagues (1963) and compared with taste thresholds of 17 healthy controls. Most strikingly in the tumour group, a heightened bitter taste and a reduction in sweet taste were noted. Thirteen patients subjectively

reported a loss of taste in addition to a meat aversion.

The dietary intake of 40 patients was assessed using five-day food diaries from which energy intake was estimated and noted as significantly lower in patients with heightened bitter taste perception. Weight loss was also associated with an altered taste acuity where despite normal intakes, it was found that 16 out of 17 patients with a reduced ability to perceive sweet taste had experienced significant weight loss (at least 2.3 kg loss in two months). Twelve patients with no recent weight loss had normal taste thresholds. The authors postulated that a lower bitter threshold was perhaps due to amino acids eliciting a bitter taste and therefore altering the plasma levels of sub-threshold stimulus and lowering threshold for bitter taste which was then translated into a dislike for a number of food items. No further investigation of the causes of altered thresholds were made. Kare and colleagues (1969) described this subjective response as a blunting of physiological reflexes. DeWys (1974) highlighted clinical implications based on these results, namely, that patients may benefit from the addition of sugar to food and that alternatives may be provided for meat products.

Ovesen and colleagues (1991) found that weight loss *per se* in cancer patients was associated with altered taste perception. In this study the forced choice technique (Henkin *et al*, 1963) was used to assess the thresholds for four primary tastes of 27 patients diagnosed with small cell lung cancer and 24 controls. Results revealed no differences in taste profiles between groups, however, within the cancer group, weight losing patients had significantly lower bitter thresholds when compared to weight stable cancer patients ($p < 0.05$). Those who responded to therapy appeared to have normal threshold profiles.

Research in an elderly cancer group needs to consider changes attributed to the ageing process (Weiffenbach *et al*, 1986). Almost two decades ago, Hill and Almli (1980) described developmental alterations in the chorda tympani nerve responses to sweet perception. Chorda tympani nerve responses to glucose and fructose increased significantly with advancing age. Murphy (1993) noted that in the elderly, a decline in taste perception thresholds had the potential to interfere with food selection and subsequent dietary intake. Most studies indicate that the elderly have reduced taste sensitivity and may also recognise and identify common odours less well (Cain and Stevens, 1989). Several decades ago, Kalmus and Trotter (1962) in a longitudinal study, found that in a period of 10 to 15 years after initial testing, taste sensitivity had deteriorated each year. Duffy and colleagues in 1995, examined the taste perception and dietary intake of 120 elderly women. In this group of patients who were nutritionally at risk, a lower olfactory perception was associated with reduced preference for the sour and bitter taste of food items and an increased intake of sugars. Interestingly, elderly women who were experiencing an alteration in taste perception also experienced less interest in social aspects of food intake.

Gee and colleagues (1988) evaluated the taste thresholds of 30 elderly and 30 young subjects using graded concentrations of standards. Vitamin intake was assessed over a 4 day period using a combination of dietary recall and food records. A positive association between the risk of low vitamin A intake and diminution of taste function was found in both age groups. In the elderly, a significant positive correlation between the risk of vitamin A deficiency and sour ($p<0.05$) and salt ($p<0.05$) was noted. However, in this study, no assessment of plasma

vitamin A was made and the accuracy of a 4 day recall method to assess vitamin status has previously been questioned (Bingham, 1991). It has been suggested that vitamin A plays an important role in taste integrity, as it is required for the synthesis of non-specific mucopolysaccharides in the epithelial cells of taste buds, an accumulation of which may impair the access of taste molecules to taste bud receptors (Bernard and Halpern, 1968). Imamine and colleagues (1990) have reported interesting results associated with a reduction in the transport protein for vitamin A (retinol-binding protein), and a reduction in taste perception.

There appears to be some debate as regards to the exact magnitude of taste aberration occurring in the elderly. This debate may be due to the difference in measurement techniques, definition of normal threshold levels, or the heterogeneity of the group (medical and nutritional status). Schiffman (1997) published a literature review of chemosensory alterations in the elderly highlighting a reduction of taste function. Age-related changes were associated with a reduction in turnover of taste buds, a poor nutritional status or certain medications which may reduce mitosis of epithelium cells, thereby altering normal taste bud physiology.

1.6.3 Assessment of gustatory perception

The main aim of techniques used to assess taste thresholds is to assess detectable differences of the amount or quality of sensory properties within a particular group. A detection threshold is the minimum value of a sensory stimulus needed to give rise to a taste sensation. A recognition threshold is the minimum value of a sensory stimulus permitting the identification of the sensation (Schiffman *et al*, 1994).

In 1963, Henkin and colleagues first described the forced choice technique for sensory perception assessment which has subsequently been widely adopted by researchers (William and Cohen, 1978; DeWys and Walters, 1975; Conger, 1973; Hall *et al*, 1980). The forced choice technique uses exponentially increasing concentrations of the tastes namely, sodium chloride for salt, sucrose for sweet, citric acid for sour and quinine chloride for bitter. For each taste, one drop of solution and two drops of placebo (distilled water) were randomly placed on the tongue. DeWys and Walters (1975) used a three-stimulus, forced choice technique to measure the detection and recognition threshold for the taste qualities of salt, sweet, sour and bitter. However, this method involves sampling of a large number of solutions, unsuitable for patients with advanced cancer.

Based on the tool by Henkin, the international standard of sensory appraisal (ISO 1991) describes a set of objective tests for familiarising assessors with sensory analysis. This method minimises any extraneous factors such as colour, temperature and odour that may disguise or equate to a taste perception. However, thresholds vary inversely with the size of the area

stimulated, smaller areas producing higher thresholds than larger areas (McBurney, 1969). This is important in patients with a dry mouth, where methods that employ a drop technique may underestimate the taste perceived. One main advantage of the International standard of sensory appraisal is the short range of concentration of stimuli used. Previous work by the current research team (Maybank *et al* 1994, unpublished data) indicates that in the elderly, a reduced range of concentrations may be used for the detection and recognition thresholds measurements.

Within a defined range of solutions, Miller and Bartoshuk (1991) highlight criterion bias in which one subject may decide that a taste is very easily noticed while another might decide that a taste was present only when they were very certain. This may be dealt with by providing the subject with water between solution to allow comparison of solution with water and therefore, ensures that the measurement is conducted from a zero baseline. In addition, McBurney and Pfaffman (1963) suggest that there may be sufficient sodium chloride in saliva to influence thresholds for NaCl. This error may be reduced by ensuring adequate rinsing of the mouth before tasting any solution.

Another technique is the up-down procedure that can be used with a variety of responses from the subject. This is a test described by Bartoshuk (1978) in which subjective responses determine the concentrations used in the assessment. If the subject indicates the presence of a stimulus, then the concentration of the stimulus is decreased in the next sample likewise, if the subject fails to indicate a stimulus, then the concentration is subsequently increased, generating a series of 'runs' of the subject's perception of the stimulus.

The use of aqueous solutions bear little resemblance to the sensory perception of food in which many compounds of tastes are present. Trant and colleagues (1982) suggested that it may be tenuous to extrapolate from simple aqueous medium to complex food items. In the study by Trant and colleagues, supra-threshold concentrations of 4 taste substances dissolved in appropriate beverages, namely, sodium chloride in tomato juice, citric acid in lemonade, sucrose in cherry drink and urea in tonic were measured. The main advantage of this technique is that it provides a framework upon which to base hedonic judgements. Ames and colleagues (1993), measured salt and sweet taste intensity in both aqueous solution and in simple foods. Six concentrations of each taste were prepared and, in addition, strained peas with six different concentrations of sodium chloride and apple sauce with sucrose were used. Taste supra-threshold intensity and pleasantness of the samples were assessed using linear scaling. A positive correlation was shown between the aqueous samples and food items.

More recently, tests have been devised incorporating real foods. Researchers in the Netherlands have studied changes in taste perception in elderly patients using a taste perception/preference test (de Jong *et al*, 1996). Four food items were used with two concentrations of each added tastes namely, potato salad (salt taste), natural yoghurt (sour taste), fruit yoghurt (sweet taste) and fruit juice (bitter taste).

1.6.4. Physiology of chemosensory perception

Taste, in addition to texture and temperature senses, combine with odours to produce a perception of flavour. Other sensory mechanisms which include taste, smell, texture, viscosity and temperature of food play a role in the regulation of gastric secretion and gastrointestinal mechanisms. In turn, alimentary signals play an important role in peripheral mechanisms of hunger, thirst and may also influence central neural mechanisms regulating food intake (Bartoshuk, 1978). Taste sensation is the experience of quality of the four primary tastes, namely, sweet, sour, salt and bitter. Additional descriptions have been used for example, umami, astringent (correlating with bitter), acrid, putrid, sapid or aromatic.

A mouth contains approximately 10,000 taste buds (Stubbs, 1989) which have a life span of approximately ten days (Beidler and Smith, 1991). Taste buds are ovoid structures located on structures of the oral cavity such as the tongue, soft palate, larynx, epiglottis, uvula and upper one third of the oesophagus. Taste buds are contained in small specialised structures called papillae (Schiffman and Gatlin, 1993) which are innervated by the chorda tympani and glossopharyngeal nerves (Mistretta, 1991). At the base of the taste bud afferent taste nerve axons invade the bud, where chemical synapses occur between serotonergic basal cells and taste receptor cells.

Cells of taste buds transform energy into neural information about the stimulus and concentration. Gustatory sensations originate in the interaction between a stimulus molecule and a putative receptor located in a taste pore at the tip of a taste bud. Hydrophilic tastes

(weak acids, sour), salts (salt and bitter), amino acids (sweet, bitter), proteins (sweet and bitter) are dissolved during mastication and reach microvillar processes of taste receptor cells by passing through saliva and the mucus layer covering the taste pore (Kinnamon and Getchell, 1991).

Taste stimulation consists of an interaction between stimulus molecules and receptor molecules producing action potentials in the nerves that supply the taste bud. After this reaction reaches an equilibrium, continued stimulation with the adapting solution will evoke no additional taste (Muller, 1991). If a flow of concentration series of a taste solution is extended across the tongue the taste is initially strong but begins to fade in seconds. Nerve fibres enter the base of taste buds and chemical synapses are formed with either the basal or nuclear region of taste cell (Kinnamon and Getchell, 1991). Messages are transmitted from taste buds to the cortex, however, some information reaches the hypothalamus, involved in feeding behaviour. The diameter of taste pores can vary because of a variety of physiological mechanisms.

Beyond the innervation of the taste cells, taste transduction describes the mechanism by which the specific type of stimulus energy is transformed into an electrical response within a specialised sensory cell. Numerous transduction pathways postulated are based on experimental evidence derived from electrophysical, pharmacological, biochemical and molecular biological studies. Transduction provides receptor cells with a means of coupling chemical stimulation to neurotransmitter release at afferent synapses. Each taste possesses its own transduction mechanism, initiated when sapid chemicals interact with sites on the apical

membrane of taste receptor cells. The membrane of the taste cell is negatively charged on the inside with respect to the outside. A taste substance causes partial loss of this negative potential resulting in depolarisation. This leads to changes in the physical characteristics of the membrane such as increased membrane permeability and an influx of sodium ions. This receptor potential generates impulses in taste fibres perhaps by secreting a chemical transmitter that stimulates nerve endings.

Olfaction plays an important part in the perception of the overall sensory quality of food items (Wysocki and Pelchat, 1993). Nerve cells, located in the superior part of the nostril are important in stimulating the olfactory system. Axons extend through a small bone called the cribriform plate to the olfactory bulb from which neurons project to the limbic area of the brain. Olfactory receptor cells are bipolar nerve cells with cilia projecting into the mucus that coats the inner surface of the nasal cavity. The cilia react with odours in the air and stimulate the olfactory cells. Odour molecules bind to the protein receptors in membranes and increase the permeability of the receptor cells, creating a receptor potential. As a result, receptor potentials depolarise cells and initiate nerve impulses.

Olfactory cells are renewed approximately every 30 days that, like gustatory receptors, renders them vulnerable to nutritional deficiencies (Schiffman, 1994). Both gustatory and olfactory perceptions play important roles in flavour and satiety. This was demonstrated by Rolls and Rolls in 1996 in which satiety was influenced by both chemosenses. In this set of experiments, satiety was influenced when food was chewed and smelled before swallowing and highlights the sensory specific neural controls on food intake.

1.6.5. Impact of treatment on taste perception

A loss of taste sensitivity results from not only anatomical changes that occur during normal ageing but also from certain diseases, pharmacological, surgical (Henkin, 1970) and radiation interventions. Altered taste perception has been associated with weight loss in patients with Autoimmune Deficiency Syndrome (Graham, 1995). In a study of 750 patients who were experiencing some form of altered taste perception, Deems and colleagues (1991) found that a blunting of taste perception in most cases reflected olfactory loss. This chemosensory dysfunction occurred in patients with a range of diagnosis including upper respiratory tract infection and head trauma.

Anecdotally, patients often associate altered taste perception with pharmacological interventions. Tamoxifen, an antioestrogen drug, used as adjunct treatment in breast cancer has been subjectively associated with dampening of chemosensory perception (McDaniel *et al*, 1995). However, Schiffman and Gatlin (1993) highlight that it is difficult to speculate on the mechanisms by which drugs alter chemosensory functions due to combined effects of pharmacological regimens. Ackerman and Kasbekar (1997) reviewed literature in the past two decades concerning drugs associated with any magnitude of alterations in taste perception. These studies included a wide range of patients namely, the elderly, chronically ill, patients with thermal injury and those with reduced appetite. Mechanisms identified as involved with sensory disturbances include damage of nerves, altered influx of calcium and other ions, chelation or depletion of tissue-bound zinc, disturbed second messenger synthesis and altered prostaglandin synthesis. The latter mechanism may also be implicated in patients with

advanced cancer who, as a result of disease mediated cytokine synthesis, may have altered prostaglandin synthesis.

An aqueous environment containing saliva is an important factor in taste perception (Spielman 1990). The main constituents of saliva are water, electrolytes, proteins and mucus required to protect mucus membrane, lubricate food and hence facilitate eating. Cations in saliva such as Na^+ and Ca^{2+} ensure adequate charge carriers to produce depolarising taste receptor potentials during taste stimulation. In addition, salivary proteins function as carrier molecules for lipophilic tastants. Although saliva itself is tasteless, salivary ions can influence taste thresholds such as, bicarbonate ions that influence salivary pH and the detection of sour modalities. Taste stimuli are known to influence saliva composition and flow. Most tastants enhance flow in a concentration-dependent manner and also alter the ion concentration. Sour stimuli, via sympathetic pathways, enhance saliva flow and the concentration of calcium ions in the saliva. Salivary glands are also susceptible to damage by radiation to the head and neck regions (Beidler and Smith, 1991). Rhodus and Brown (1990) suggests that one in five elderly patients, xerostomia was associated with a reduction in taste perception. Sodium (Na^+) is reported to influence the taste threshold of Sodium chloride (NaCl). Lower thresholds of sodium have been noted in experiments after rinsing the mouth (Kinnamon and Getchell, 1991).

Galili and colleagues (1978) studied short-term alterations in salivary secretion with pharmacological agents and subsequent food preference behaviour. This animal study demonstrated that a reduction in saliva flow resulted in changes indicative of a change in taste

perception. On the contrary, Christensen *et al* (1984) found that reduced saliva flow caused no major changes in taste thresholds except for minimal changes related to sour taste modality. This later study does not support previous results, perhaps due to the different methods used to alter saliva flow. More recently, Fox (1987) noted large discrepancies between the subjective feeling of a dry mouth and objective changes in salivary gland dysfunction. In addition, Weiffenbach and colleagues (1986) found that objective and subjective measures of taste perception were unaffected by saliva function. In relation to the effects of radiotherapy, Congor (1973) suggests that chemosensory changes are a side effect resulting from either the direct effect of radiation on salivary glands reducing saliva flow or due to the direct effect on nerve and taste cells which are also affected by radiotherapy. A more recent study by Backstrom and colleagues (1995) found that in 35 patients who received radiation to the head and neck regions symptoms, a dry mouth was frequently reported and associated with a poor dietary intake. Within the hospice setting, there is evidence to suggest that these taste changes occur in patients not receiving any such treatment.

1.6.6 Nutritional status and taste perception

A number of studies have implicated undernutrition as a causative factor in producing alterations in taste perception. This is not surprising as a high turnover rate of cells may be influenced by nutrient supply. This was demonstrated by Ohara and colleagues (1994) where a impaired taste perception was evident during protein malnutrition in rats. The authors related zinc depletion to changes in the length of papillae surrounding the taste buds. Zinc is required for the synthesis and activity of salivary protein gustin that plays a role at taste bud

receptor level (Henkin, 1994). Heyneman (1996) demonstrated that zinc supplementation in daily doses of 25-100mg was an efficacious treatment for taste dysfunction secondary to zinc depletion. However, the authors highlight that there was not sufficient evidence to suggest treatment in patients with altered taste perception that do not exhibit low serum zinc concentrations. In disease where the inflammatory response is triggered, redistribution of zinc and possibly albumin will occur and this low zinc in plasma may be reflecting disease and not nutritional status. Low nutrient intake or altered protein metabolism mediated by pathophysiological levels of cytokines may reduce the synthesis of both of these transport protein (Chevalier, 1995) and the consequent reduction in these essential micronutrients at cellular level may cause taste abnormality.

Bernard and Halpern (1968) identified a role of vitamin A in taste transduction mechanisms. In animals who were vitamin A deficient, the nerve activity evoked by tastes applied to the tongue was reduced by 50%. This suggested that vitamin A plays a role in mucopolysaccharide synthesis at taste reception level. Vitamin A plays an important role in the integrity, growth and differentiation of epithelial tissue found in taste buds (Gershoff, 1981). In a study by Biesalski and colleagues (1985), guinea pigs supplemented with vitamin A free diet over 90 days, showed morphological changes in the mucous membrane of cells. In vitamin A deficiency, papillae in which taste buds are embedded were altered, shortened and showed squamous cells covering the epithelium. Taste buds were hindered by a dense layer of squamous cell resulting in a loss of sensitivity during deficiency. Interactions exist between many vitamins and minerals. Smith and colleagues (1973) demonstrated the requirement for zinc in maintaining the normal concentration of vitamin A in plasma. In this clinical study,

three groups were either fed a diet deficient in vitamin A and zinc, a diet supplemented with vitamin A and deficient in zinc or a diet supplemented with vitamin A and zinc. For the group supplemented with vitamin A only, liver levels of vitamin A were the highest but serum levels were half of the group supplemented with vitamin A and zinc.

Despite the number of studies conducted examining the relationship between nutritional status and taste perception, there appear to be no consistent results. This may indeed be due to the variation in the characteristics of patients between groups, the heterogeneous nature of the groups, the presence of metastatic disease, the selection of appropriate control groups and the measurement of taste perception. It is tenuous to extrapolate results from simple aqueous medium to complex food media. Kamath and Booth (1983) suggested that thresholds cannot be used to assess the relative sensory intensity as food contains tastes in concentrations higher than those of threshold values. Therefore in an attempt to examine the true clinical picture, researchers have begun to explore the selection of foods which result from complicated recognition by senses of smell and taste. Neilsen and colleagues in 1980 noted that in a large group of cancer patients (n 133), reported alteration in taste perception was associated with the incidence of other nutritional-related symptoms. Almost all patients with reported altered taste perception (80%) and 49% of other group also experienced early satiety. In addition, 70% patients with altered taste perception and only 37% patients with no alterations in taste experienced anorexia.

Other nutrition-related symptoms have been associated with altered gustatory perception. Brush and Halpern (1970) hypothesised that gastric distension may modify the gustatory perception. Gastric distension affects the efferent activity in the chorda tympani and glossopharyngeal nerves that mediate taste responses via central connection of gastric vagal fibers.

1.6.7 Mediators of the malignant disease process and altered taste perception

Nutritional deficiencies and side-effects of treatment may not fully explain alterations in taste perception. The lack of any single nutrient consistently correlating with taste perception indicates that causes of altered taste perception are multifactorial. Many studies have reported changes in one or two taste modalities solely and not a uniform change as would be expected in sensory damage to taste cells. One of the main unanswered questions relates to the mechanisms whereby one taste modality is altered.

Recently, animal studies have yielded interesting results in this area. Smith and colleagues (1994) examined the preferences of tumour bearing and non-tumour bearing rats for 5 chemical tastes. Over 300 rats were provided with a 2- bottle test from which a liquid was selected (taste solution or water) from day 3 after implantation of tumour until death. Both groups equally avoided quinine hydrochloride and hydrochloric acid solution, indicating that the tumour growth produced no disruption in taste perception. However, a difference was observed in the preference for sucrose solution. The tumour bearing rats maintained a high preference for sucrose and saccharin until approximately 20 days, which then decreased with

advancing tumour growth. A reduction in calorie intake preceded the changes in sucrose and saccharin preference by several days. Altered preference for sweet but not salt taste suggests food related taste cues may be more susceptible to the development of taste aversions during tumour growth. This study demonstrated that experimental tumours may induce a decline in food intake, resulting from a change in taste perception.

Other work suggests that a peripheral site may also be involved and that sensory nerves may be mediators of reduced dietary intake associated with cachexia. Exton and colleagues (1995a) demonstrated that taste aversions are a manifestation of the inflammatory response. Bernstein (1994) showed that $\text{TNF}\alpha$ alone may be responsible for the induction of anorexia and learned food aversions. Work by Goehler and colleagues (1995) investigated the direct effects that cytokines such as $\text{IL-1}\beta$ and $\text{TNF}\alpha$ exert on the brain. Their work demonstrated that in animal studies, subdiaphragmatic vagal transection attenuates conditioned taste aversions induced by $\text{IL-1}\beta$ and $\text{TNF}\alpha$ and also blocked both $\text{IL-1}\beta$ and $\text{TNF}\alpha$ induced pain and fever. This suggests that cytokines modulate neural activity via the activation of vagal afferents. This work supports the theory that cytokines may play an important role in the avoidance of novel tastes with which they have been paired (conditioned taste aversions). Cytokines appear to alter central nervous system function either by direct cytokine entry into the brain via active transport processes at circumventricular organs at which the blood-brain barrier is weak, or by indirect influences via the induction of central signals subsequent to binding to cerebral vascular endothelia (Moltz 1993), or by peripheral action through activation of afferent nerve activity. Indeed, peripheral processes exclusive of central processes influence taste receptor function. Similarly, other workers have shown that in

disease, endotoxins, mainly lipopolysaccharide, are responsible for many symptoms such as fever and inflammation (Bret-Dibat *et al*, 1995; Sehic and Blatteis, 1996). In addition, endotoxins stimulate macrophages to release both eicosanoids and cytokines that may cross the blood brain barrier and subsequently activate neural processes (Watkins *et al*, 1995). In an animal model, chorda tympani (CT) section in conjunction with activation of the inflammatory response by lipopolysaccharide did not cause any diminished response to sodium taste perception which is the normal response to this CT section (Phillips and Hill, 1996). This suggests that the immune system ameliorates the effects of combined chorda tympani section and dietary sodium restriction. Immune modulation of taste afferent nerves has not been assessed in animals without CT section.

Taste information is conveyed from the taste receptors to the brain stem via afferent pathways (Hermann *et al* 1983). Cytokines may be responsible for the activation of afferent neural pathways, altering afferent information and hence enhancing perception of peripheral sensation. The altering of pathways has been implicated in pregnancy induced sickness (Brewin, 1980). Andrews and Whitehead (1990) suggested that hormones may sensitise the area postrema that receives inputs from visceral afferents and subsequently stimulates emetic pathways. Likewise, abnormal neural activity was associated with altered taste perception in a case reported by Miller and Bartoshuk (1991). Following removal of the right chorda tympani nerve, salty taste was heightened, despite no stimulation of the taste buds. This afferent nerve was stimulated without the activation of sensory receptors or normal transduction mechanisms.

From the literature, several aspects of flavour perception in cancer patients have not been fully explored. A limited number of studies in the palliative care setting have investigated the prevalence and magnitude of altered taste perception. However, little is known of the impact of altered taste perception on dietary intake, food choice, nutritional status and QOL in palliative care. The exact mechanism by which gustatory and olfactory changes occur remains elusive. This data would prove pivotal in the appropriate nutritional management of chemosensory aberrations, an integral component of palliative care.

1.7. Study Hypotheses

This study concentrates on patients with advanced cancer, examining gustatory and olfactory perception. The impact of gustatory perception on quality of life, nutritional status and dietary intake is explored. In addition, the relationship between blood cytokine concentrations and gustatory perception are investigated with the following null hypotheses.

Null Hypothesis (1): There is no difference in the gustatory thresholds of the 4 primary taste (sweet, sour, salt and bitter) between patients with advanced cancer and age matched controls.

Null Hypothesis (2): There is no difference between the olfactory perception of patients with advanced cancer and age matched controls.

Null Hypothesis (3): There is no relationship between gustatory perception and quality of life in patients with advanced cancer.

Null Hypothesis (4): There is no relationship between gustatory perception and nutritional status in patients with advanced cancer.

Null Hypothesis (5): There is no relationship between gustatory perception and dietary intake in patients with advanced cancer.

Null Hypothesis (6): There is no relationship between gustatory perception and blood cytokine concentration and gustatory perception.

2.1 Subjects

Patients with a histologically proven diagnosis of cancer admitted to St. Columba's Hospice, Edinburgh were assessed for inclusion to the study. Prior to recruitment, information sessions were held within the Hospice to increase awareness of the study as prospective research had not previously been conducted in this environment. Staff were provided with information regarding the study objectives, recruitment criteria and the use of assessment tools within a terminally ill group of patients.

Control subjects of similar age were recruited from a geriatric assessment unit at St. John's Hospital, Livingston, W. Lothian. For the purposes of distinguishing the two sample groups in the subsequent chapters, they will be referred to as cancer patients and control subjects.

2.1.1 Inclusion criteria

The inclusion criteria for cancer patients and control subjects were as follows:

- i. Age ≥ 18 years.
- ii. Willingness to participate as indicated by signed informed consent (Appendix 4). This was obtained from patients and subjects prior to conducting any study related procedure.
- iii. Patients scoring at least 8 out of 10 on the abbreviated mental test were included in the study (Jitpunkel *et al*, 1991; Appendix 5).

In addition, for cancer patients:

- i. A clinical diagnosis of cancer.

2.1.2 Exclusion criteria

The exclusion criteria for cancer patients were as follows:

- i. Patients currently or six weeks after receiving chemotherapy, radiotherapy or drug treatment for oral *Candidiasis* were excluded from the study as these treatments are known to have a significant effect on taste perception (Mossmand and Henkin, 1978).
- ii. Patients in severe distress or deemed unsuitable for inclusion by medical staff due to either an increase in symptom severity or shortened time to death.

For the control subjects:

1. Patients with a CRP concentration $>10\text{mg/l}$ were excluded.

The first line of selection was whether all of the inclusion criteria and none of the exclusion criteria were met. The selection process subsequently incorporated the opinions of medical and nursing staff regarding patient suitability.

2.2 Ethical considerations

Ethical approval was granted by the Medical and Oncology sub-committee of Lothian Health Board (Appendix 1). All data processed were identified by patient number, thereby ensuring that the patient's identity remained unknown.

Communicating in a sensitive manner on an on-going basis ensured that the patient's decision regarding their participation was respected. Following identification of suitable patients, contact was made by a member of the nursing staff who informed the patient of the study and enquired if they were interested in participating in the study. Prior to consenting, information regarding study procedures was provided by the researcher (Appendix 3). Patients were free to withdraw from the study at any time, hence acknowledging their autonomy.

Research in the palliative care setting has been aptly described as a 'minefield' with regard to ethical issues (Brewin, 1986; DeReave, 1994). During the study design, inherent limitations of assessment tools within this study population were acknowledged. The philosophy of hospice care in maximising QOL was paramount when choosing methodologies. The length of time required to complete an assessment, the ease and comfort in doing so were considered key issues in selecting appropriate methodology. Methods that are inconvenient, uncomfortable, unsuitable for bedridden subjects, time consuming or requiring large amounts of equipment are unsuitable for patients with advanced cancer .

2.3. Nutritional assessment

2.3.1 Weight

For research purposes, patients were weighed in light indoor clothes using portable scales (Wylex scale, accuracy to 0.2 kg) and informed of their weight on request.

Control subjects were weighed in light indoor clothing on admission and thereafter at weekly intervals (Wylex scale, accuracy to 0.1 kg). Body weight was compared with age and sex specific ‘ideal’ weight tables (Lehmann *et al*, 1991). Changes in weight reported by patients and controls were noted as an indicator of recent changes in body composition.

2.3.2. Body mass indices

Reference values for both demiquet (males) and mindex (females) were used as indices to compare weight with height. (Lehmann *et al*, 1991).

For Females: (Mindex) $= \frac{\text{kg}}{(\text{demispan})^2 \text{m}^2}$

For Males: (Demiquet) $= \frac{\text{kg}}{(\text{demispan}) \text{m}}$

Demispan was used in the calculation to derive demiquet (males) and mindex (females). For the measurement of demispan, a measuring tape anchored between the middle and ring fingers was extended along the outstretched arm to the sternal notch. The arm was horizontally abducted in neutral flexion, the wrist in neutral rotation. The metal tape was fitted at the zero point with a button connected with shirring elastic, which anchored it between the fingers. Measurements were made to the nearest 10mm. Regression equations produced by Bassey (1986) for estimating height from demispan, for both males and females were used. Height was calculated to the nearest 0.01m

Females: Height (cm) = 1.45 x demispan (cm)) + 60.1

Males: Height (cm) = (1.40 x demispan (cm)) + 57.8 (Bassey, 1986)

2.3.3 Triceps skinfold thickness

A measurement was made of TSF with the subjects arm relaxed at the side. The elbow was flexed at 90 degrees with the palm facing superior. The tape was positioned perpendicular to the long axis of the upper arm and the maximum circumference was recorded on the non-dominant arm (Shimokata *et al*, 1989). TSF was measured on the posterior aspect of the arm, over the triceps muscle at a point midway between the lateral projection of the acromium process of the scapula and the inferior margin of the olecranon process of the ulna. Skinfolts were picked up with the thumb and index finger along the axis of the upper arm and measurements taken using calipers (Holtain Ltd., Pembrokeshire, UK). With the calipers exerting a constant pressure at varying openings of the jaws, the width of opening was read off

on a scale incorporated in the apparatus. The mean value recorded from three measurements was compared with age and sex reference data (Burr and Philips, 1983).

2.3.4. Arm muscle circumference

From the measurement of TSF, a record was made of the arm circumference (MUAC) taken at the midpoint between the lateral projection of the acromium process of the scapula and the inferior margin of the olecranon process of the ulna. AMC (mm) was calculated using the following formula derived from Gurney and Jelliffe (1973):

$$AMC \text{ (mm)} = MUAC - [\pi \times TSF(\text{cm})]$$

$$\pi = 3.14$$

The measurements were compared with age and sex specific reference data (Burr and Philips, 1983).

2.3.5. Arm muscle area

Arm Muscle Area (mm²) was derived from AMC using the following formula derived from Gurney and Jelliffe (1973):

$$AMA \text{ (mm}^2\text{)} = \frac{[AMC(\text{mm})]^2}{4\pi}$$

The results expressed as cm^2 , were compared with age and sex specific reference data (Burr and Philips, 1983).

2.3.6 Hand grip dynamometry

Hand grip strength was measured by a single spring hand held dynamometer using the non-dominant hand. Patients were asked to press the dynamometer in one hand and readings were taken when the maximal grip strength was reached. In the dynamometer, movement of the free end of a coiled tube moves in response to an applied force which is transmitted through a lever system to a lightweight pointer on a kilogram scale (Klidjian *et al* 1980). Three readings were taken (a three minute rest period between readings) and the highest value recorded. Results were compared with reference standards derived from the assessment of 184 mobile independently living elderly subjects (65-90years) in England (Pearson *et al*, 1985). The presence of any physical disability of the hand such as rheumatoid arthritis was noted, as these conditions may affect the interpretation of results.

2.3.7 Bioelectrical impedance analysis (BIA)

BIA involves the passage of a small alternating electric current (50kHz) through the body between the wrist and the unilateral ankle. The corresponding voltage was measured by an analyser (RJL Systems, Detroit, USA) to assess the impedance (ratio of voltage to current). A four electrode technique was used with one pair of electrodes for passing current into the body

and another pair serving as the resulting voltage drop (Foster and Lukaski, 1996). Assuming a constant hydration of lean tissue, resistance and reactance of the current is used to determine total body water using the equation from which lean body mass was derived (Fearon *et al*, 1994). Subsequently, by subtraction from calculated lean body mass, fat mass was estimated as follows:

$$\text{FFM (kg)} = (0.671 \times 10^4 \times H^2/R) + 3.1S + 3.9$$

Where H = Height (m), R = Resistance Ω , S = Gender Female (0) Male (1)

($r = 0.94$, SEE = 3.1 kg)

2.4 Clinical assessment

For all subjects, the following relevant medical history, obtained from medical notes, was documented prior to nutritional and chemosensory assessment:

- i. Diagnosis. For cancer patient this included tumour type, previous aggressive treatment, time since diagnosis, presence and site of any metastatic disease,
- ii. Drug regimens (medication prescribed regularly and as required)
- iii. Other relevant metabolic pathologies such as diabetes mellitus.

2.5 International standard for sensory appraisal of gustatory perception

Principle of technique

The principle of the International Standard for Sensory Appraisal lies in the presentation of aqueous solutions corresponding to certain taste qualities, at a given concentration and in a known order. All substances are water-soluble in order to impart specific taste (Birch and Westwell 1994). This tool assesses taste acuity by measuring detection and recognition thresholds and assesses taste sensitivity by measuring intensity scaling of more concentrated tastant (Drewnowski, 1997).

Method of determining taste thresholds

The procedure for determining taste thresholds used an ascending series in which the subject was presented with increasing stimulus concentrations until the subject reported that it was detected and subsequently recognized. Before beginning the assessment, subjects rinsed their mouth with water at room temperature. A 20ml sample at the lowest concentration of the first taste solution was presented to the subject, who was instructed to rinse the fluid around the entire oral cavity. Solutions of increasing concentrations were presented in turn. The subject then assessed whether the sample tasted differently from water. If so, the subject was asked to describe the taste (recognition). A wide variety of terms were acceptable to describe the tastes for example, acid, sharp, tart, citrus and vinegar were all considered acceptable for the sour taste of citric acid.

Tasteless, still and odourless water was used to cleanse the palate and to prepare dilutions. Stock Solutions were prepared using the listed solutions (table 2.1) derived from food-grade reference substances. Test solutions were prepared from the fresh stock solution on the day of testing according to the concentrations given below:

Caffeine (Bitter Stimulant) Concentrations: 0.015mM, 0.03mM, 0.06mM,
0.12mM, 0.24mM, 0.48mM

Sodium Chloride (Salt stimulant) Concentrations: 1.5mM, 3mM, 6mM, 12.5mM,
25mM, 50mM

Citric Acid (Sour Stimulant) Concentrations: 0.075mM, 0.15mM, 0.3mM,
0.6mM, 1.2mM, 2.4mM

Sucrose (Sweet Stimulant) Concentrations: 1.5mM, 3mM, 6mM, 12mM,
24mM, 48mM

To avoid distraction, the assessments were conducted in a private room or quiet area of the ward. Between each taste sample, subjects were presented with water to cleanse the palate. In order to avoid sensory fatigue, 3-5 minutes were allowed between each stimulus tested. Assessments were performed on two occasions to prevent fatigue but within 24 hours, following the same time interval after mealtimes. In addition, patients were asked whether they had noticed any changes in their taste perception.

Table 2.1 Specification of taste stock solution

Taste	Reference food grade substance	Concentration g/l
Bitter	Crystallized caffeine (monohydrate) M = 212.12	0.54
Salt	Anhydrous Sodium Chloride M = 58.46	4.00
Sweet	Sucrose M = 342.3	24.00
Sour	Crystallized citric acid (monohydrate) M = 210.14	1.20

M = Molarity

2.5.1 Modification of assessment tool for use in elderly advanced cancer patients

The length of time to complete assessments is an important consideration when selecting methodology for use in patients with advanced cancer. The international assessment of sensory appraisal involves assessment of 24 solutions. In order to prevent tiredness, increase compliance and accuracy a shorter modified version of the test is more appropriate in this patient population.

Subjects

The international standard of sensory appraisal was performed on a group of elderly patients attending a Geriatric assessment unit, St.John's Hospital, W.Loathian (n=18, 8M:10F, mean age = 72 ± 4.5 years).

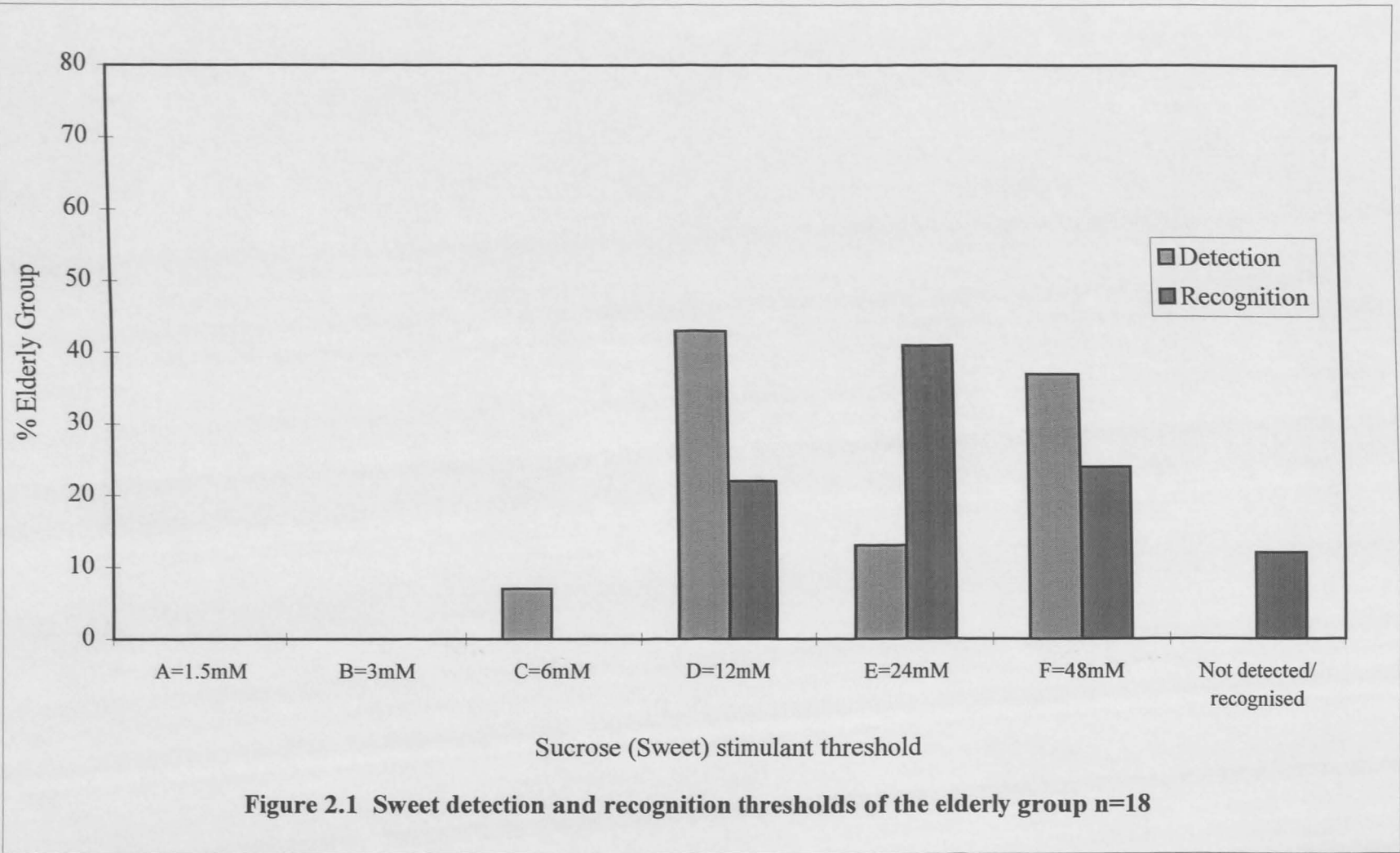
Method

The test was performed on 2 occasions, assessing the gustatory threshold profiles of 2 tastants at each occasion. On each occasion, the test was performed in a quiet part of the ward in order to minimize any distractions. Detection and recognition thresholds of the 4 primary tastes, namely, sweet, sour, salt and bitter were assessed.

Results

Figure 2.1-2.4 show the taste profiles for the 4 tastants at 6 different concentrations. For each tastant the lowest concentrations were neither detected or recognition by patients. Therefore in order to shorten the test, the following 4 higher concentrations may be used:

	Threshold Score			
	1-----	2-----	3-----	4-----
Bitter (Caffeine)	0.6 mM	0.12 mM	0.24 mM	0.47 mM
Sweet (Sucrose)	6 mM	12 mM	24 mM	48 mM
Sour (Citric acid)	0.3 mM	0.6 mM	1.2 mM	2.4 mM
Salt (Sodium Chloride)	6 mM	12.5 mM	25 mM	50 mM
Increased Concentration of Taste ----->				
Decreased Sensitivity of Taste ----->				



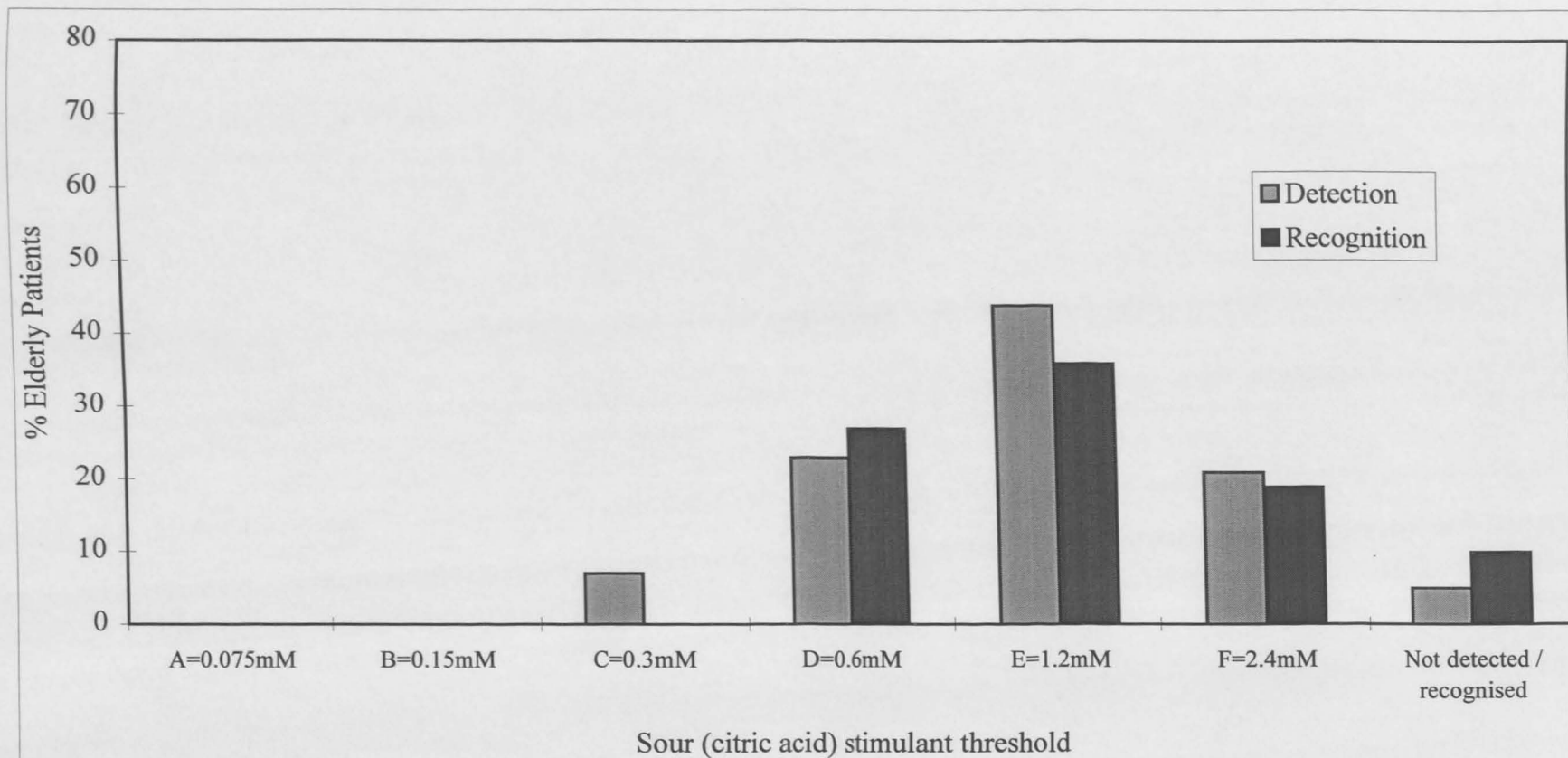


Figure 2.2 Sour detection and recognition thresholds of an elderly group n=18

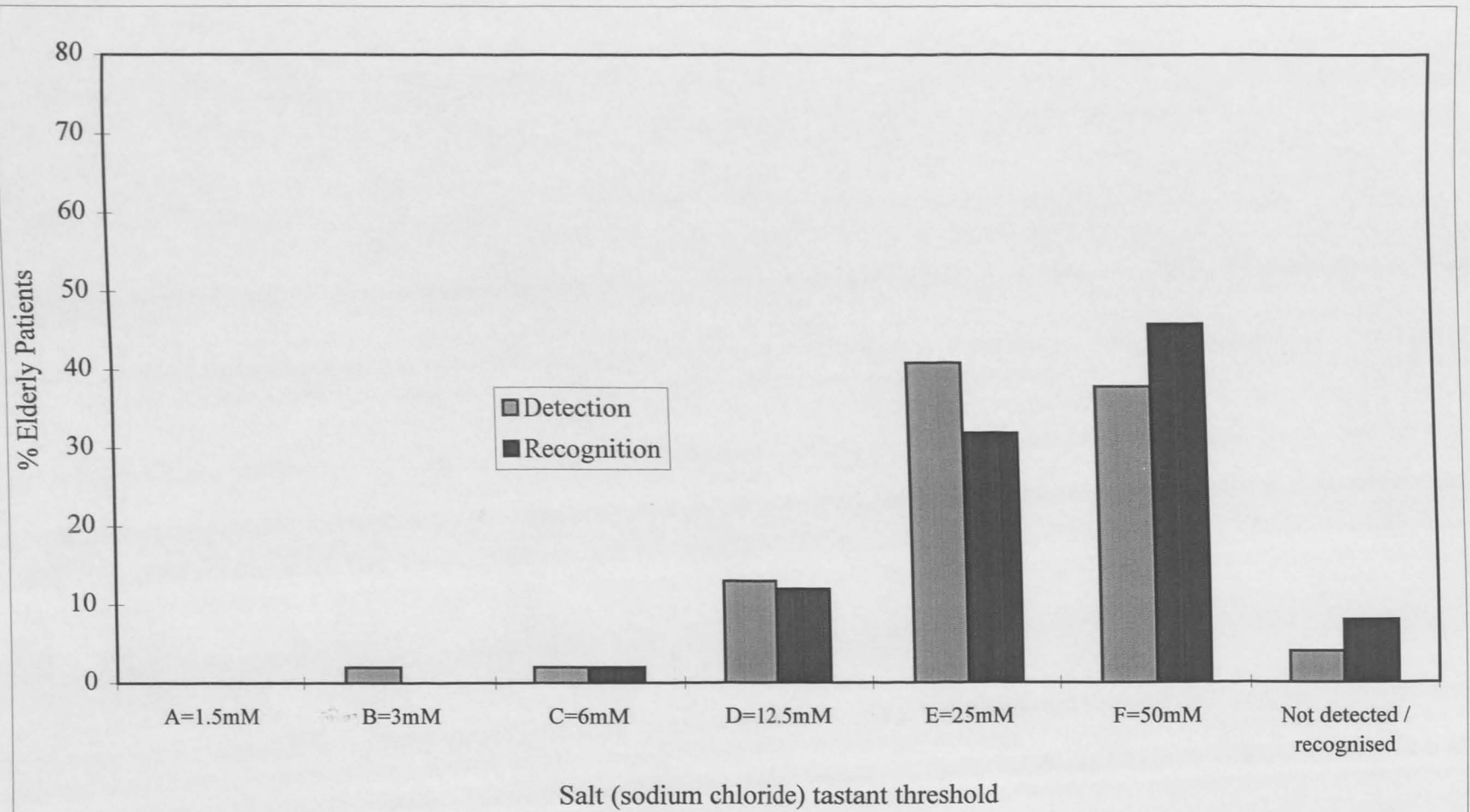


Figure 2.3 Salt detection and recognition thresholds of an elderly group n=18

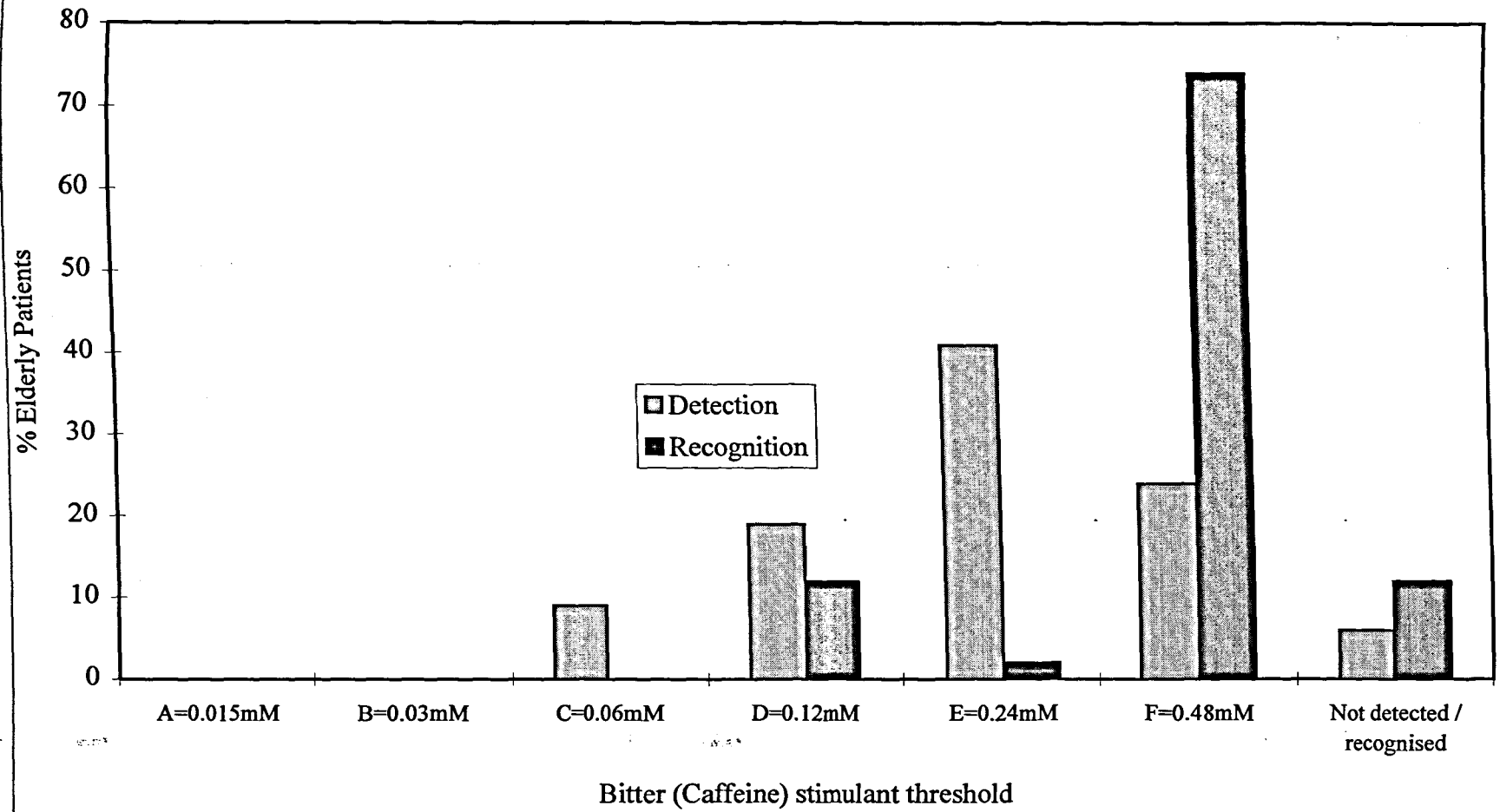


Figure 2.4 Bitter detection and recognition thresholds in an elderly group

2.5.2 Comparison of threshold ranges for an elderly and a young group

In the literature, there is considerable evidence to suggest that the elderly have higher gustatory thresholds than younger counterparts. As described in section 2.1, patients attending a geriatric assessment unit were recruited to act as a control group. Comparing the gustatory thresholds of an elderly group and a younger adult group assessed the appropriateness of using an elderly control group in this current study.

Subjects

Eighteen patients were recruited from the Geriatric assessment unit, St.John's hospital, W.Loathian (8M:10F, mean age 72 ± 4.5 years). Fifteen adults were recruited from Queen Margaret University College, Edinburgh (5M:10F, mean age 29 ± 3.6 years). None of the elderly group were acutely ill and none of the adult group were smokers.

Methods

The International standard of sensory appraisal was used to determine the detection and recognition thresholds of both groups. Within the geriatric assessment unit, the test was performed in a quiet part of the ward to avoid any distractions and performed at the same time of the day. For the adult group, the test was performed in a sensory appraisal laboratory, likewise, to minimize any distractions that would interfere with the subject's gustatory perception. Gustatory thresholds (sweet, sour, salt and bitter) were analysed using the Mann-Whitney test to compare data of the 2 independent groups.

Results

Figures 2.5-2.8 show the thresholds ranges of both the elderly and adult groups. For the detection of all 4 tastants, the elderly group exhibited higher thresholds as compared to the younger adults ($p < 0.05$). In addition, the elderly exhibited higher recognition thresholds for sour and bitter tastants ($p < 0.05$). These results indicate that the elderly experienced a blunting of their taste perceptions as compared to the younger counterparts.

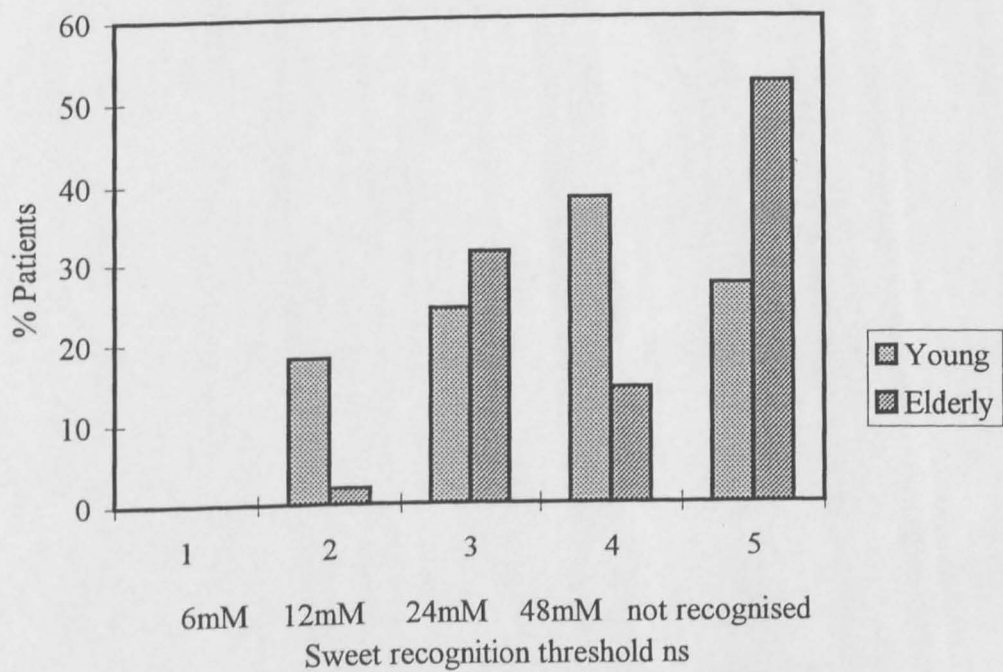
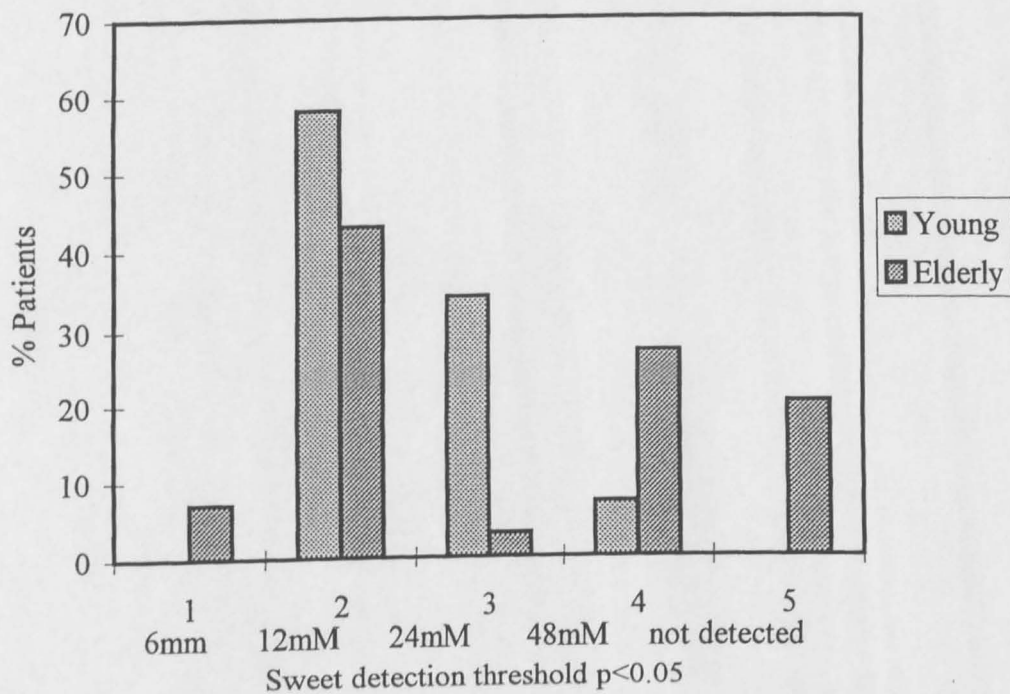


Figure 2.5 Comparison of sweet perception thresholds of elderly controls and younger adults

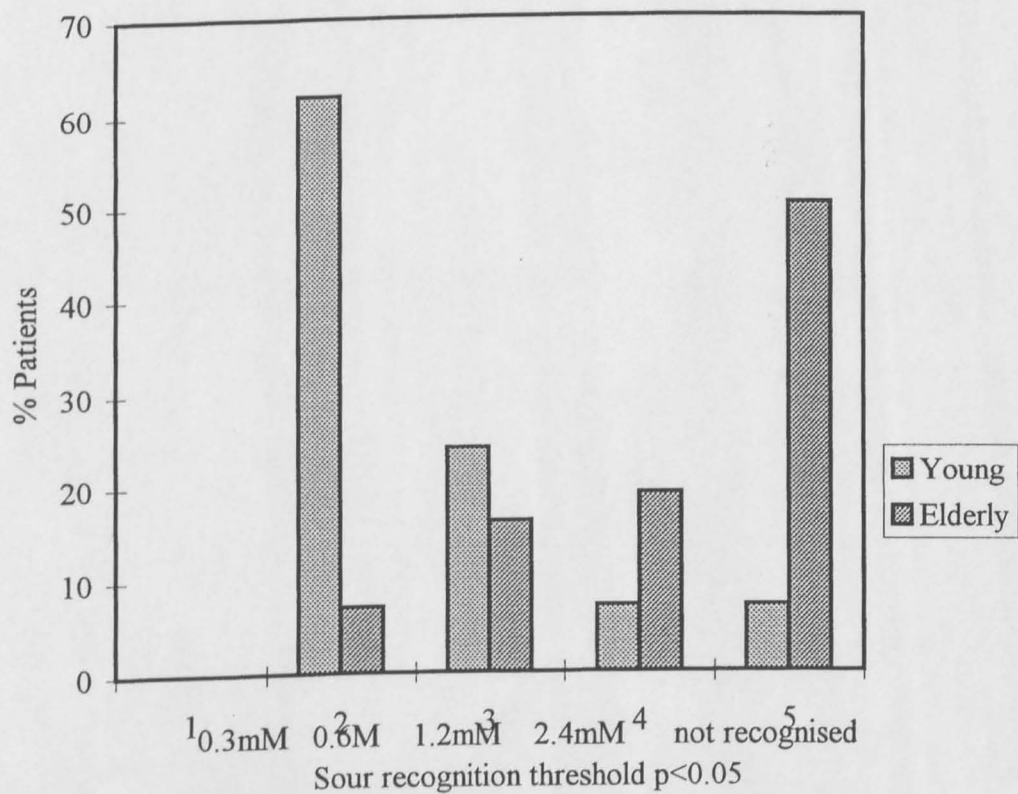
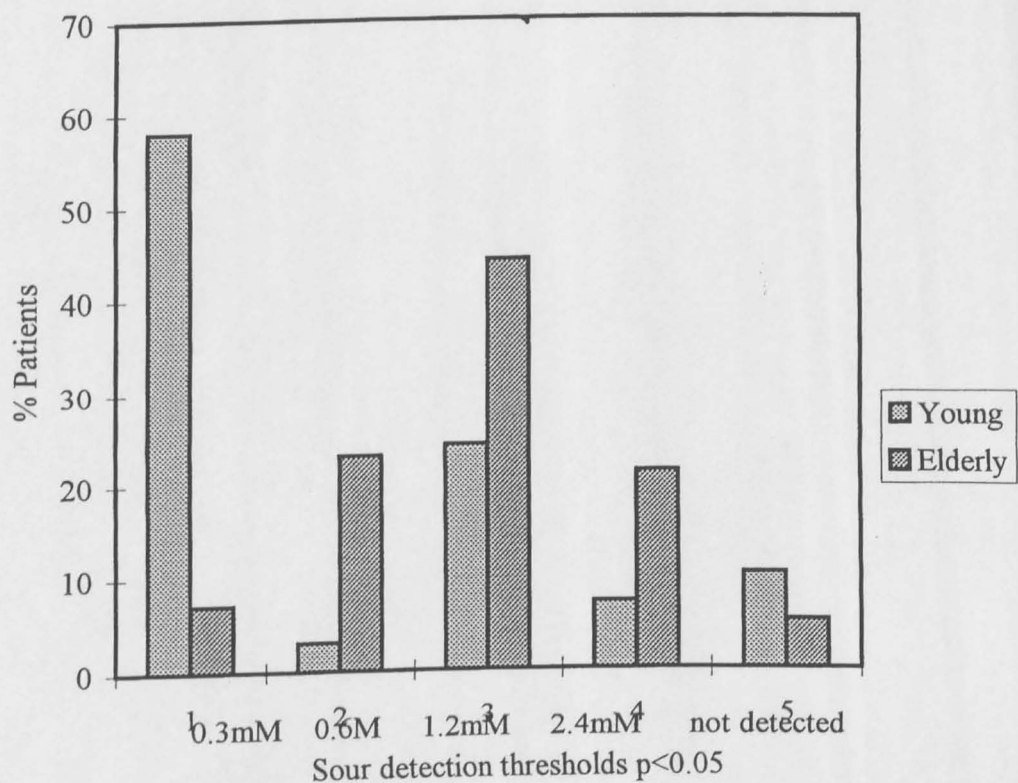


Figure 2.6 Comparison of sour perception threshold of elderly controls and younger adults

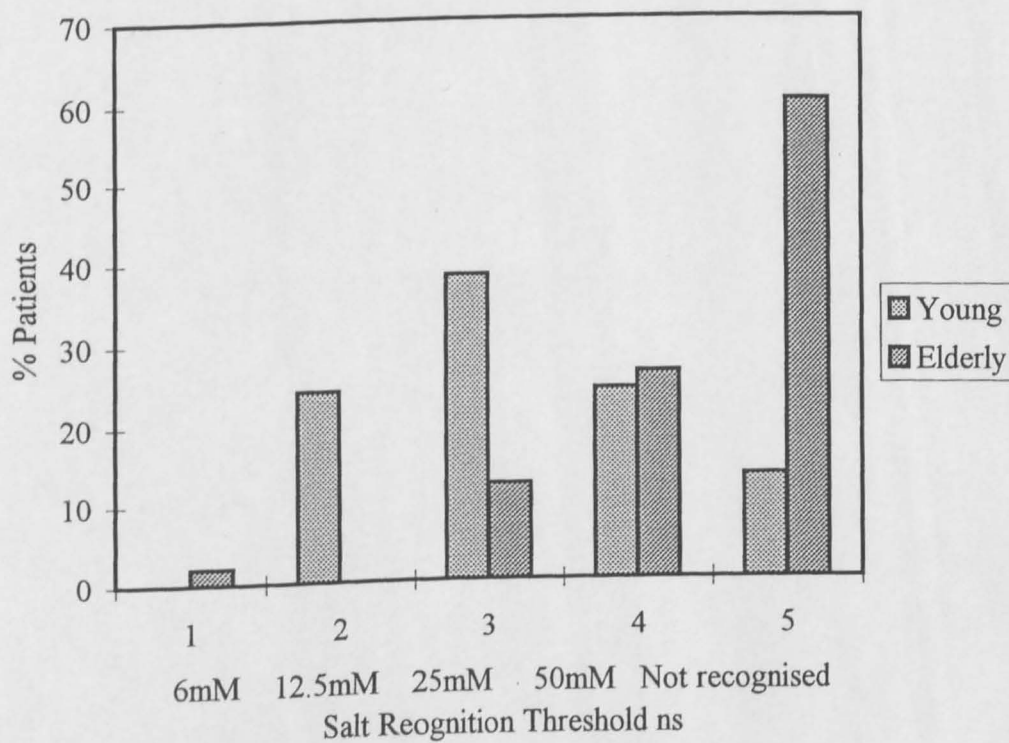
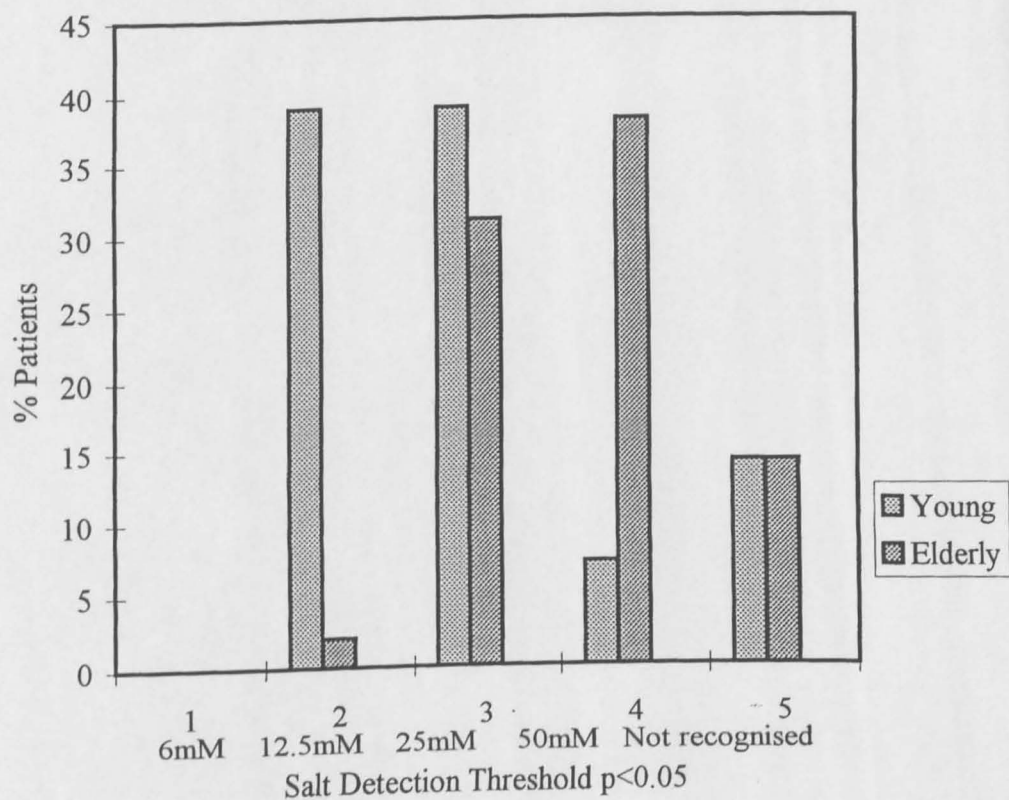


Figure 2.7 Comparison of salt perception thresholds of elderly controls

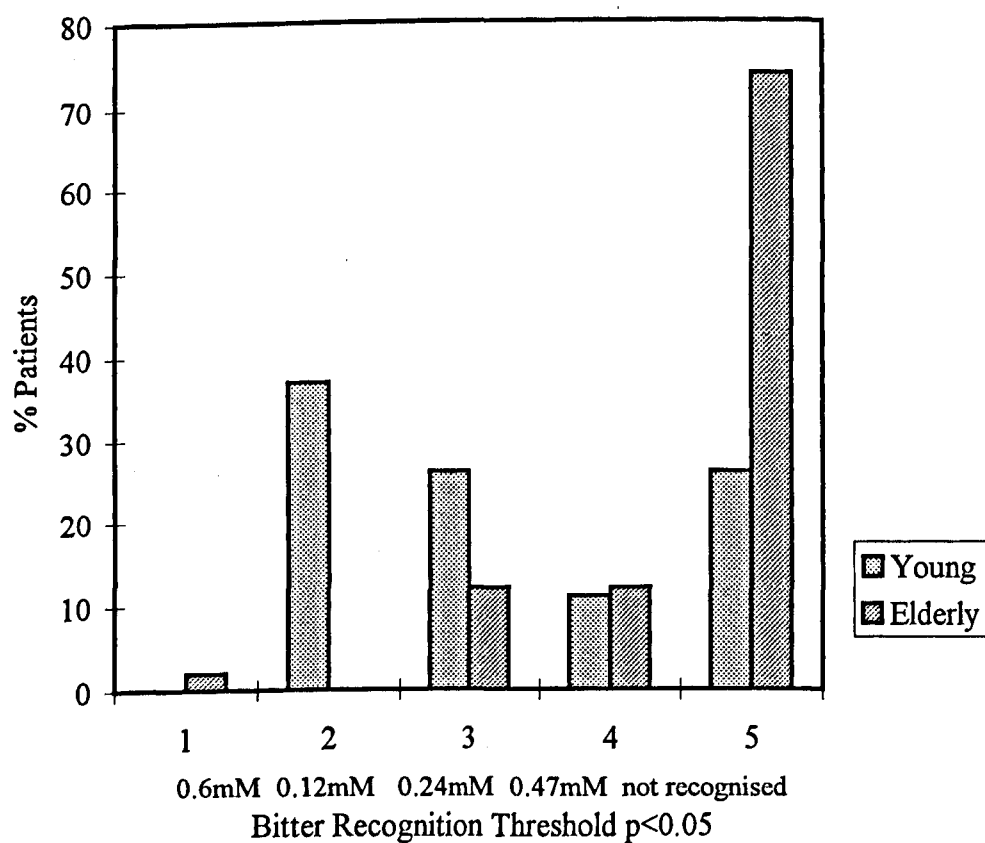
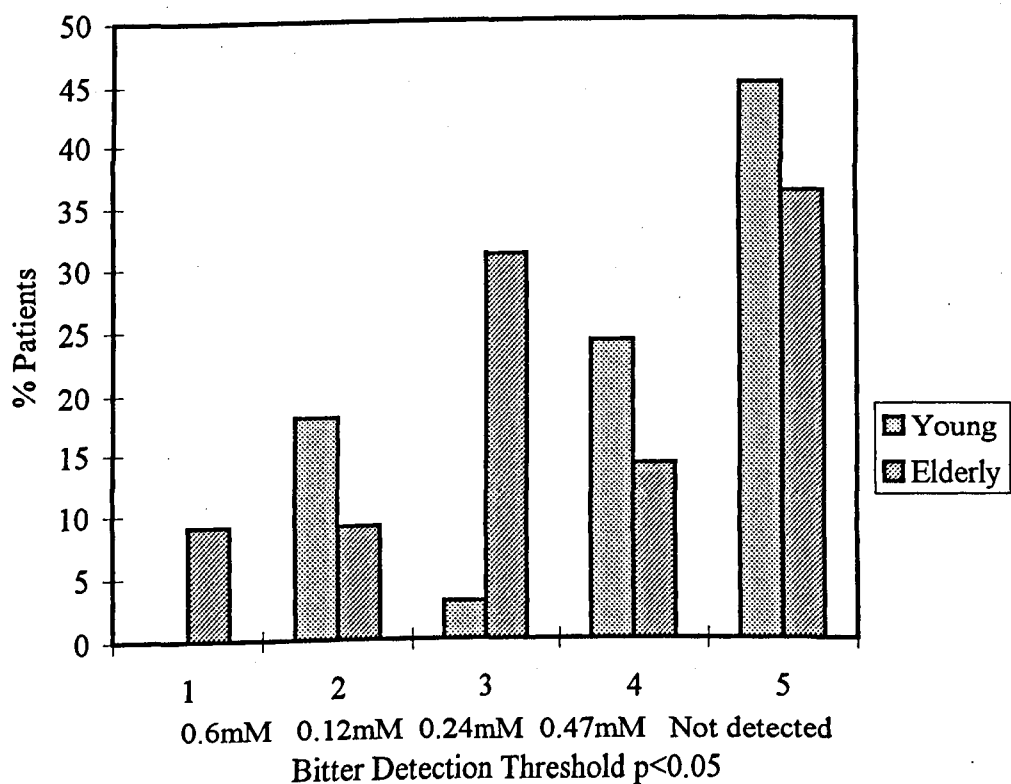


Figure 2.8 Comparison of bitter perception thresholds of elderly controls and younger adults

2.5.3 Intra-subject repeatability for each tastant.

As highlighted in chapter 1.6.3, the international standard of sensory appraisal used to determine taste profiles is potentially susceptible to intra subject error. It is therefore necessary to perform pilot study to determine the reliability of the subjects perception of gustatory perception.

Subjects

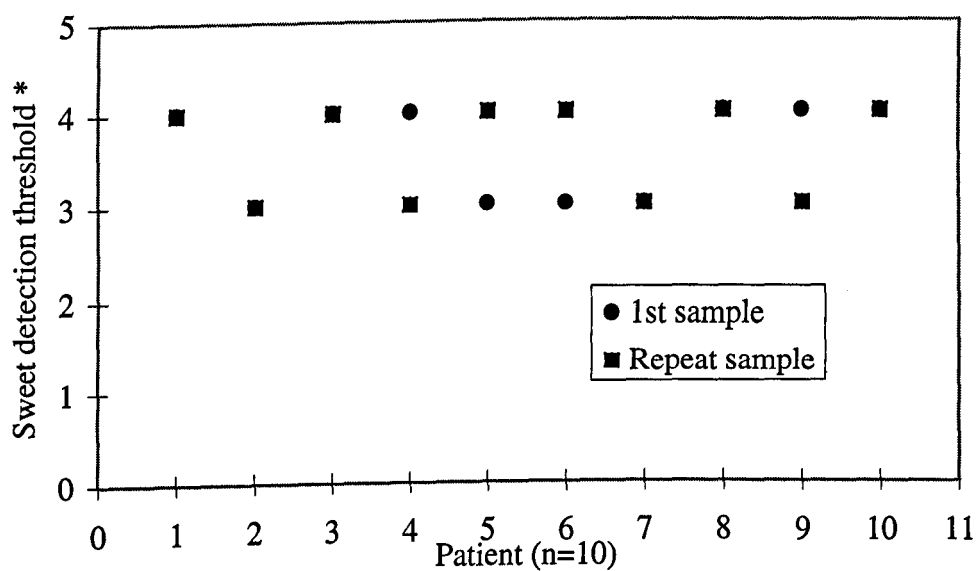
Ten subjects were recruited from Queen Margaret University College, Edinburgh (5M:5F, mean age 27 ± 2.5 years).

Methods

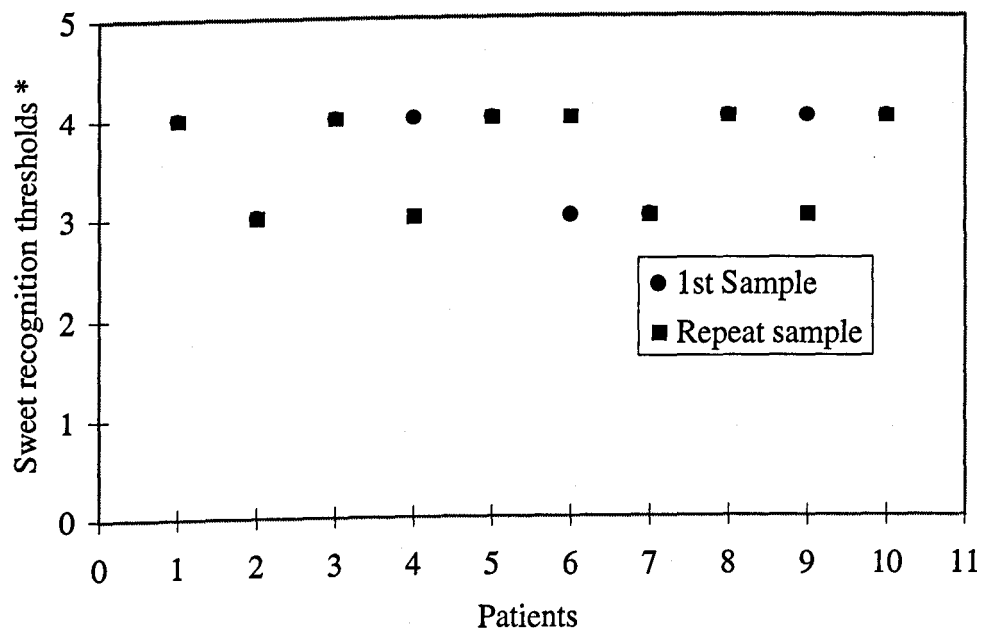
The International standard of sensory appraisal was performed on 2 separate occasions at the same time of the day with a 7-day period. The gustatory test was performed under standard conditions, in a sensory appraisal laboratory. Repeated thresholds were analysed using spearman's correlation coefficient.

Results

The sensory rating for both the detection and recognition profiles are shown in figure 2.9-2.12. For the detection and recognition of all 4 tastants, no significant differences were noted between the 2 repeated samples. The results indicate that there was no significant difference between the repeated assessments.

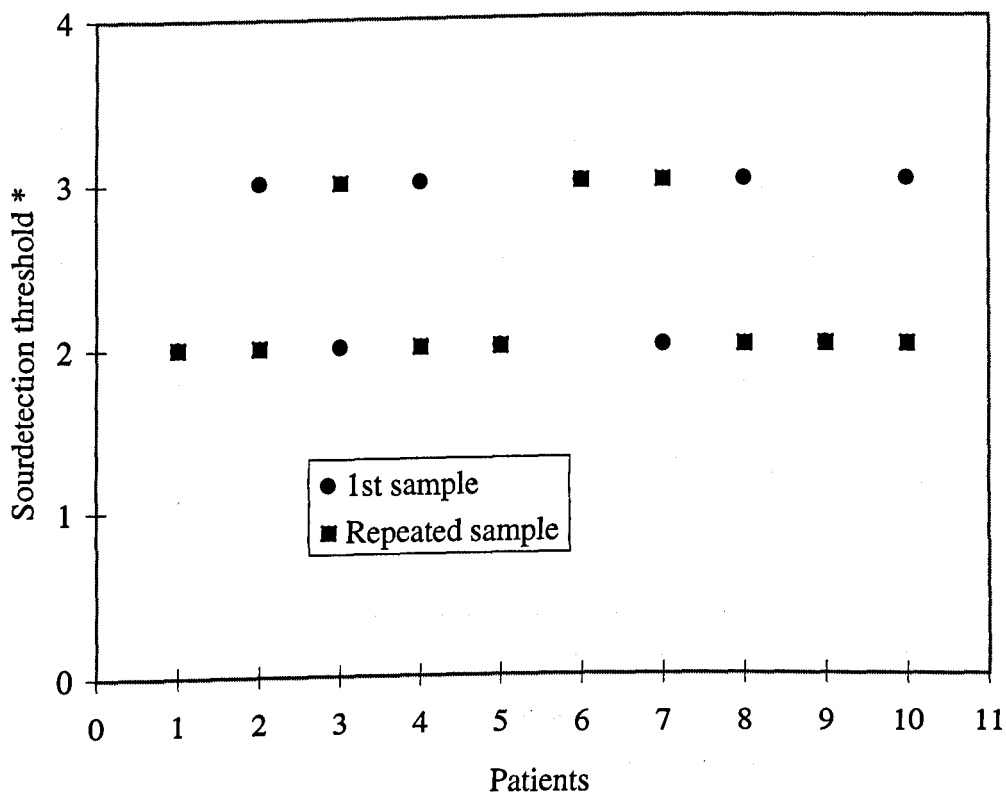


* Detection thresholds 1=6mm, 2=12mM, 3=24mM, 4=48mM, 5=not detected

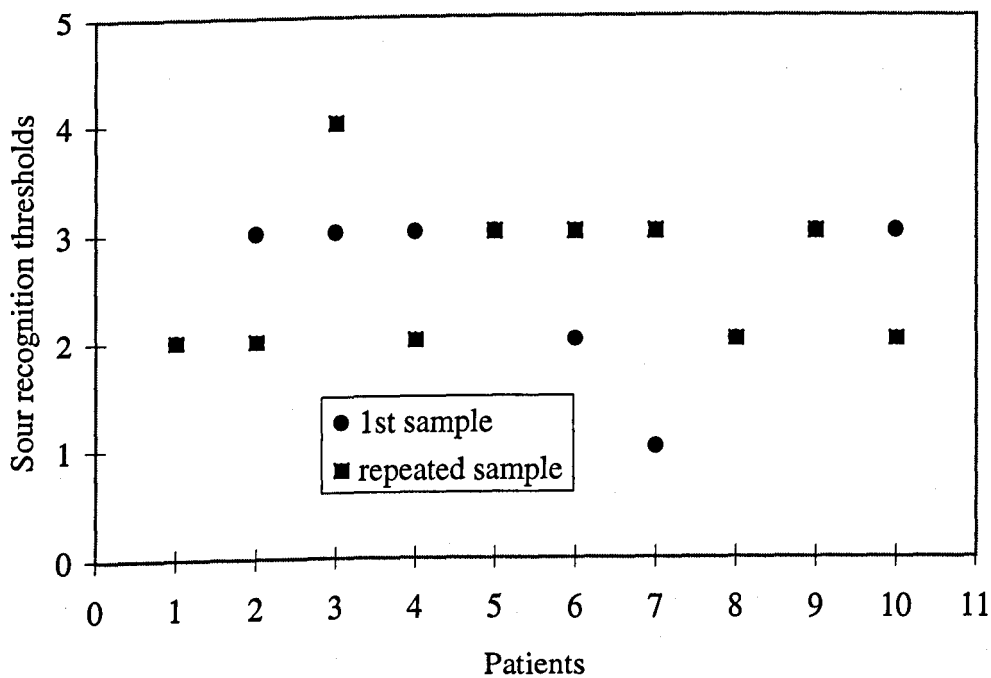


* Detection thresholds 1=6mm, 2=12mM, 3=24mM, 4=48mM, 5=not detected

Figure 2.9 Repeated measurements of sweet thresholds



* 1=0.3mM, 2=0.6mM, 3=1.2mM, 4=2.4mM,



* 1=0.3mM, 2=0.6mM, 3=1.2mM, 4=2.4mM

Figure 2.10 Repeated samples of Sour thresholds

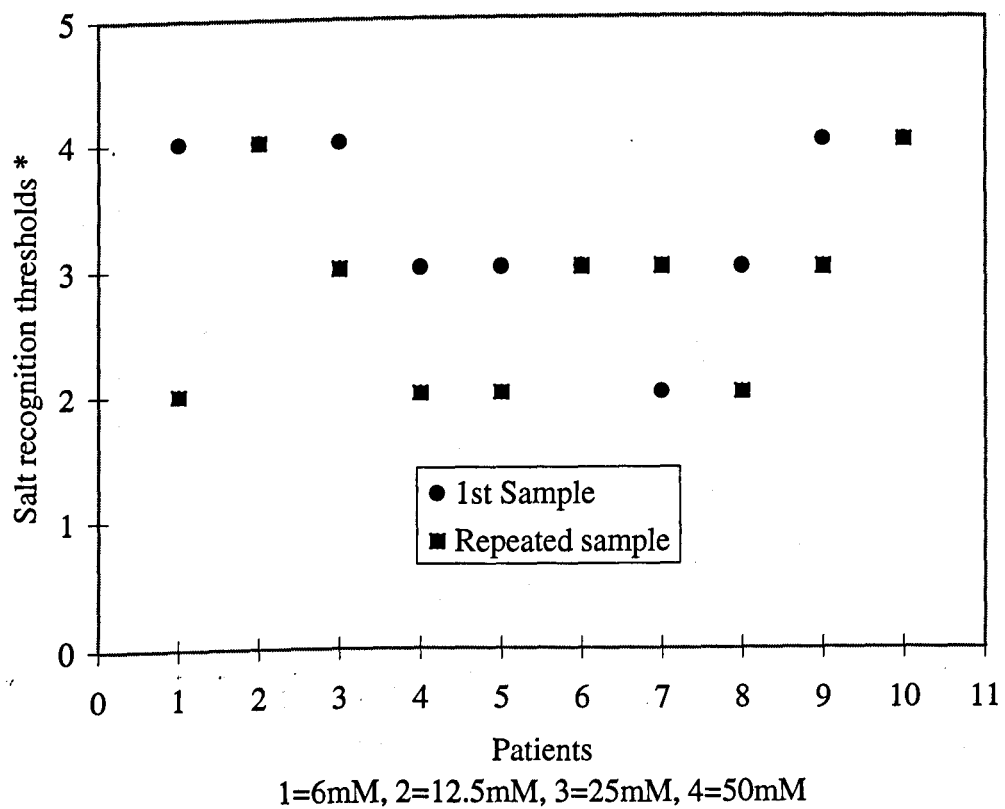
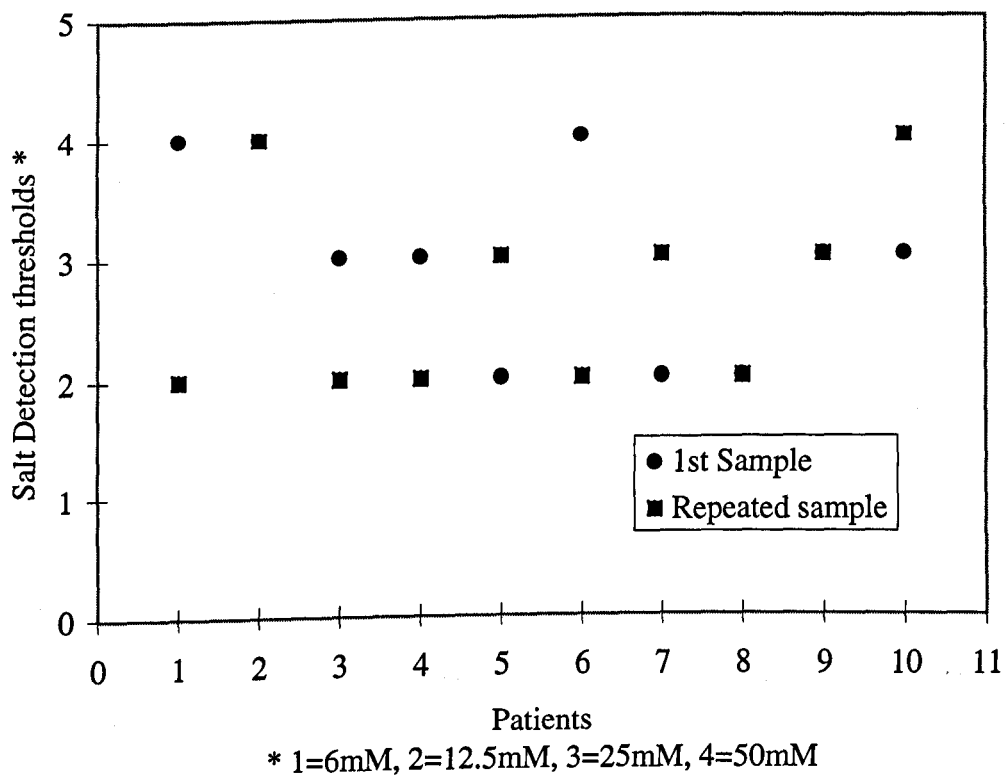
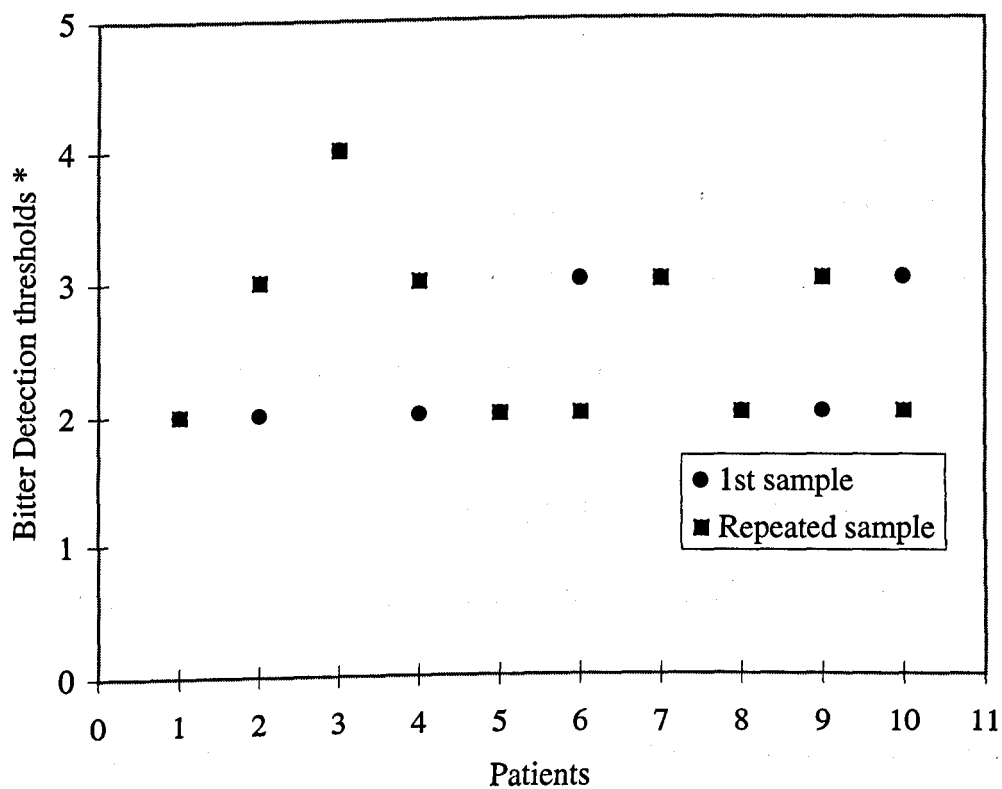
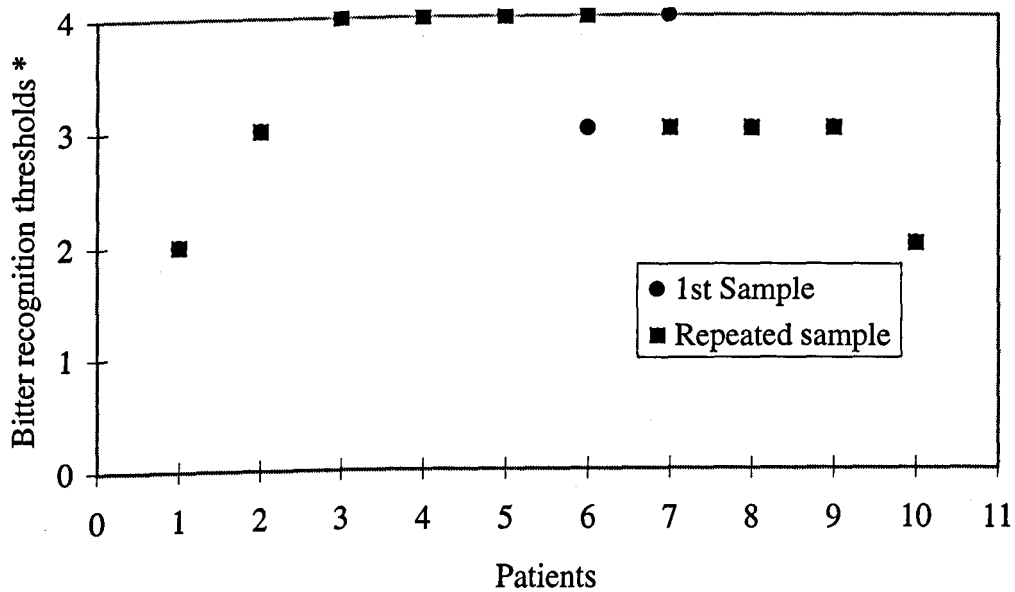


Figure 2.11 Repeated samples for Salt thresholds



*1=0.6mM, 2=0.12mM, 3=0.24mM. 4=0.47mM



*1=0.6mM, 2=0.12mM, 3=0.24mM. 4=0.47mM

Figure 2.12 Repeated samples for bitter perception

2.6 Assessment of olfactory perception

A simple and non-invasive qualitative assessment using common everyday odours to assess olfactory acuity and recognition was used (Schiffman, 1994). Patients and controls were screened using the abbreviated mental test (Jitpunkel, *et al*, 1991) which allowed for the inaccuracy of recognising an odour due to memory loss.

A small sample of each odour was placed in individually labelled bottles. Subjects were presented with each odour bottle and instructed to identify each odour with one minute intervals between assessing the contents of each bottle. The following odours were assessed in the same order for each patient: Citrus, Garlic, Ammonia, Menthol, Iso-amyl Acetate (pear drops), Benzaldehyde (Almonds), Vanilla, Acetic Acid (Vinegar), Germolene, Eugenol (Cloves). For each odour detected and identified, a score of 1 was given. Alternative responses were acknowledged as correct for odours, for example, the smell of lemons were noted as a correct response for citrus odour.

2.7 Dietary intake assessment

2.7.1 Subjective assessment of symptoms influencing dietary intake

An assessment of commonly occurring oral and gastrointestinal symptoms was made based on a subjective global assessment (SGA) tool. This was previously designed for use in patients with cancer to assess the impact of nutritional support on nutritional status and QOL (Ottery, 1995; Appendix 7). In addition, a record of any pharmacological intervention was made.

2.7.2 Objective assessment of dietary intake

Within the hospice, patients were provided meals from a bulk system of food provision in which the type and quantity of food was chosen at each meal time. Within the geriatric assessment unit, although the meals were provided by a pre-plated system, the control subjects had a choice of food items and portion sizes. The three day weighed intake technique was used for the estimation of food consumed. This involved weighing food presented to the patient and thereafter weighing any food uneaten. Food items provided by visitors were also included in this assessment. Nutrient intake of the quantity of food consumed was then estimated using a dietary analysis package (Compeat, Nutrition Systems, London).

Dietary intakes were compared with Dietary Reference Values (Department of Health, 1991):

Energy (Daily Reference Value):

Male 65-74years=10MJ, >75years=9MJ

Female 65-74years =8MJ, >75years =7MJ)

Protein (Reference Nutrient Intake)

Male 65-74years =60g, >74years =54g

Female 65-74years =60g, >75years =69g.

Estimated energy requirements were calculated from the estimating Basal metabolic rate (BMR) using the Schofield equation (Schofield, 1985) and applying an appropriate physical activity factor (PAL, Department of Health, 1991): Estimated energy requirements = BMR x PAL PAL (x1.3) was selected for patient and controls with a sedentary lifestyle.

Schofield equation for calculating BMR:

$$30-60 \text{ years} \quad \text{BMR (men)} = (0.048 \times W) - (0.011 \times H) + 3.670 \quad (\text{sem} = 0.7)$$

$$\text{BMR (women)} = (0.034 \times W) + (0.006 \times H) + 3.530 \quad (\text{sem}=0.466)$$

$$\text{Over 60 years} \quad \text{BMR (men)} = (0.038 \times W) + (4.068 \times H) - 3.491 \quad (\text{sem}=0.66)$$

$$\text{BMR (female)} = (0.033 \times W) + (1.917 \times H) + 0.074 \quad (\text{sem}=0.43)$$

W = Actual of usual weight (kg)

H = Height (cm)

A = Age (years)

2.7.3 Assessment of food selection

The reporting of any changes in food selection associated with altered taste perception was recorded. Patients were asked specifically if they experienced any changes in their taste perception (Appendix 7). Alterations in food selection associated with altered taste perception were assessed by means of the two open-ended questions:

Have you noticed any changes in the taste of food or drink? YES / NO

Have you noticed any changes in the smell of food or drink? YES / NO

2.8 QOL assessment

Within this current study, an interview style questionnaire was based on validated questions from the Hospital Anxiety and Depression Scale (HAD scale; Zigmond and Snaith, 1983). The tool was extensively reviewed by senior medical and nursing staff before implementation on the ward. In addition, it was piloted on three patients attending the Day hospice to firstly, assess the length of completion and secondly, assess the ease of answering the questions. Feedback was received at all stages of the study design period and used to modify the tool (Appendix 6).

Reflection during research for people who are facing emotional pain in terminal stage of their illness may be a distressing experience (de Raeve, 1994). Within the context of this research, an interview was used to provide a structured assessment within a supportive environment as to not distract from the QOL of the patient or interviewer. The interview was performed by two observers, a nurse lecturer in palliative care with experience working with terminally ill patients and the researcher. Responses from subjects were allocated to one of five categories. The first set of questions was posed to subjects reporting altered taste perception and all patients responded to the second section of question. The assessment of the impact of altered taste perception on quality of life was not performed on the control group. The tool outlined above was modified from the HAD for use in patients with advanced cancer and not a healthy elderly group. Although there is a lack of information regarding comparison between both groups, it was beyond the scope of this study to validate the use of the tool in both groups to provide meaningful data for comparison.

2.9 Biochemical analysis

2.9.1 Cytokines

Principle of assay

Plasma cytokine concentration were measured by the ELISA (enzyme linked immunoassay) method. This assay employs the quantitative sandwich enzyme immunoassay technique were a monoclonal antibody specific for a cytokine has been pre-coated onto a microtiter.

Blood sampling

EDTA- anti-coagulated blood was obtained from patients. Plasma was obtained by centrifugation at 3000 rpm for 10 minutes. After collection, samples were stored at -20°C until batch analysis could be performed in order to reduce interassay error. Serum analysis of TNF α , IL1 β and IL6 were performed with commercial ELISA kits (R&D Systems Europe, Oxfordshire, UK).

Immunoassay procedure

The following components were brought to room temperature and prepared: wash buffer, substrate solution and cytokine standard. All samples and standards were assayed in duplicate using the following technique:

1. 50 μ l assay diluent was added to each well.
2. 200 μ l standard or sample was added to each well and incubated for 2 hours at room temperature. Any cytokine present in the sample was bound by the immobilized antibody.
5. Wells were aspirated and washed 3 times plate.
6. 200 μ l conjugate (enzyme-linked antibody specific for cytokine) was added to each well and incubated for 2 hours at room temperature.
7. Wells were aspirated and washed 3 times.
8. 200 μ l substrate solution was added to each well and incubated for 20 minutes at room temperature. The colour developed in proportion to the amount of cytokine bound in the initial stage
9. 50 μ l stop solution was added to each well to stop the colour development.
10. Intensity of cytokine bound was measured by optical density of each well was determined within 30 minutes using a microtiter plate reader set to 450nm wavelength correction.

Construction of standard curve

The average reading was made from duplicate readings, from which, the average zero standard of optical density was subtracted. Optical density for the standards and the concentration of the standards were used to produce a standard curve. The concentration of cytokines in each sample was determined from the standard curve.

2.9.2 Serum albumin

Bloods samples taken through routine blood letting were spun and processed. Serum albumin was measured using an automated bromocresol green dye binding technique. This was performed at accredited laboratories at the Western General Hospital, Edinburgh and St. John's Hospital, Livingston, Lothian.

2.9.3 Serum CRP

CRP was used to assess the presence and the magnitude of an on-going acute phase response. A CRP measurement of $> 10\text{mg/l}$ was taken as an indication of a positive acute phase response (Thompson *et al*, 1992). A competitive binding immunoassay method was used to analyse CRP in serum. This method allowed a tracer labeled antigen and the antigen in the sample under investigation to compete for binding sites on the antibody molecules. When competitive binding occurs, the more tracer-antigen complex that binds to the antibody molecule, the less tracer-antigen complex that remains in solution. If a sample contains a high concentration of the antigen, after the competitive binding reaction reaches a steady state, there is a low concentration of bound tracer in the reaction mixture and polarization is low. The precise relationship between polarization and concentration of the unlabelled protein in the sample is established by measuring the polarization values calibrated with known concentration of the protein. Using the polarization values generated for each sample in the assay, the concentration of protein in known samples were calibrated using the stored calibration curve.

The assays were performed at St. John's Hospital, Livingston, Lothian and Western General Hospital, Edinburgh.

2.10 Data evaluation and statistical considerations

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS, version 6.6). To assess the prevalence and magnitude of altered taste perception in patients with advanced cancer, the variables of subjective taste and smell perception were assessed using descriptive and qualitative analysis. The objective measures of chemosensory function (thresholds ranges 1-4) in the unpaired cancer and control groups were analyzed using Mann-Whitney test. Subjective reporting of changes in taste perception between the cancer and control groups was compared using Chi-squared analysis.

Comparison of taste perception, nutritional status and dietary intake between the cancer and control groups was determined using a student t-test. QOL and food selection data were analyzed using Chi-squared analysis. In addition, the relationships between mediators of the disease process, CRP and taste perception were established using t-test and correlation coefficient analysis.

Extreme data points were determined by plotting box plots (SPSS, version 6.6). Outliers were identified as values more than 1.5 box-lengths from 25th and 75th percentiles.

3.1 Introduction

Null Hypothesis (1): There is no difference in the gustatory thresholds of the 4 primary tastes (sweet, sour, salt and bitter) between patients with advanced cancer and age matched controls.

Null Hypothesis (2): There is no difference between the olfactory perception of patients with advanced cancer and age matched controls.

The following chapter explores both the gustatory and olfactory profiles of patients with advanced cancer (n=56) compared to age matched controls (n=42). Both subjective and objective measurements of gustatory and olfactory perceptions are made.

The international standard of sensory appraisal (ISO 1991) was used to determine the detection and recognition thresholds of four primary tastes (sweet, sour, salt and bitter). A common food odours test was used to provide an indication of the olfactory perception. Open-ended questions were asked to capture information about the cancer patients (n=50) and control subjects (n=42) perception of their gustatory and olfactory chemosenses.

3.2 Results

3.2.1 Demographic Data

Patients with advanced cancer

Patients with advanced cancer admitted to St.Columba's Hospice for palliative care were assessed for inclusion to the study. Written informed consent was obtained from 56 patients who fulfilled all of the inclusion criteria. Reasons for admission to the hospice ward included symptom control (n=38; 68%), respite care (n=9; 16%) and continuing care (n=9; 16%).

Histologically proven primary tumour diagnosis and presence of any metastatic disease in patients are shown in figure 3.1. Mean age of these patients was 72.4 ± 9.7 sem years (range 50-91 years). Fifteen male (27%) and 41 females (73%) were recruited, the former predominantly presented with large bowel (colon and rectum, n=5) and prostate (n=3) carcinoma. Whereas, for females, the main primary tumour diagnosis was breast (n=12), large bowel (colon and rectum, n=10) and ovarian carcinoma (n=6) (Table 3.1).

Control Group

A comparable control group, comprising 46 patients admitted to a Geriatric Assessment Unit were recruited (20 Male, 26 Female). A reduction in mobility was the main reason for admission to the Geriatric Assessment Unit (Table 3.2). The mean age of the patients was

77.9 \pm 6.3sem years (range 66-91 years). This hospitalised control group had no indication of an on-going inflammatory response as confirmed by measurement of serum CRP (mean CRP 5.2 \pm 0.5sem mg/l; range <1.5-9.0mg/l). Of these patients, seven were admitted to the Geriatric Assessment Unit for the management of a urinary tract infection. However, they exhibited no elevation in CRP, which was performed within the assessment period and were therefore included in the analysis. Apart from the 46 patients, an additional two control subjects were excluded as an elevated serum CRP was noted.

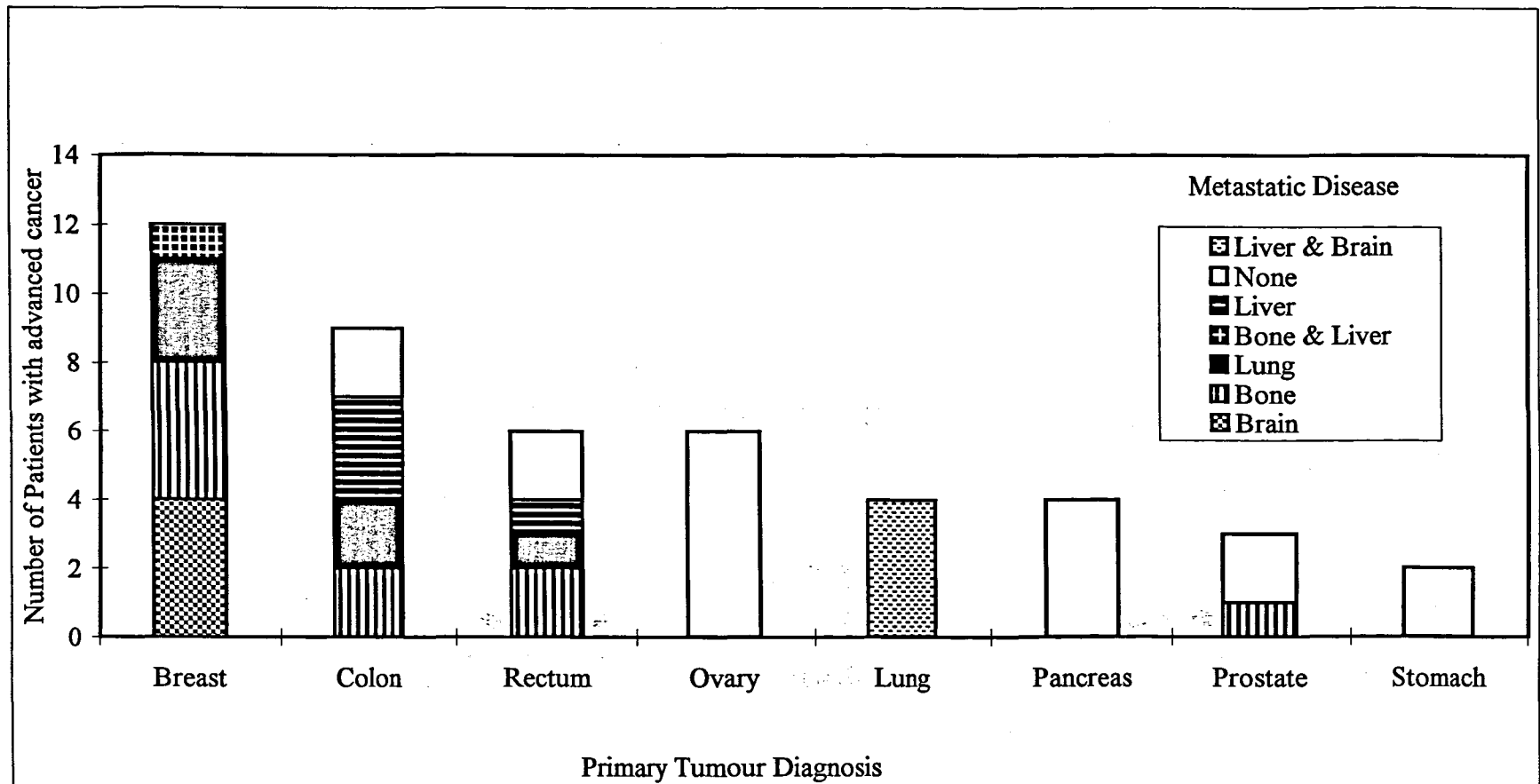


Figure 3.1 Distribution of primary tumour diagnosis and metastatic disease in patients with advanced cancer

Table 3.1 Classification of cancer diagnosis of male and female cancer patients

Male Patients (n=15)			Female Patients (n=41)		
Primary Tumour	n	% male sample	Primary Tumour	n	% female sample
Prostate	3	20	Breast	12	29
Rectum	3	20	Colon	7	17
Colon	2	13	Ovary	6	15
Lung	1	7	Rectum	3	7
Bile Duct	1	7	Lung	3	7
Pancreas	1	7	Pancreas	3	7
AML	1	7	Kidney	2	5
Stomach	1	7	Stomach	1	2
Ceacum	1	7	Oesophagus	1	2
Unknown	1	7	Liver	2	5
			Unknown	1	2

Table 3.2 Reasons for admission to the Geriatric Assessment Unit (Controls)

Reason for Admission	n	% Controls (n 46)
Reduced Mobility (rehabilitation)	27	59
Urinary Tract Infection	7	15
Leg Pain	5	11
Osteoarthritis Assessment	4	9
Other	3	2

3.2.2 Taste perception profiles

From the standard dilution taste test (International standard for sensory appraisal, ISO1991), detection and recognition profiles for the primary tastes (sweet, sour, salt and bitter) were derived. The concentration at which each primary taste was detected and recognised was quantified on a scale rating 1 to 4, where 1 indicated the lowest concentration of taste likewise, threshold number 4 represented the strongest concentration. The number of patients not detecting or recognising the tastant at thresholds 1-4 was also noted. Mann-Whitney non-parametric test was used to analyse the difference in taste thresholds between the cancer and control groups.

For both cancer patients and control subjects, the recognition and detection profiles for each primary taste are shown in figures 3.2 to 3.5. Significant differences were noted between both groups with respect to the recognition and detection thresholds of bitter taste modality (Figure 3.2). Cancer patients had a lower threshold for bitter detection ($p < 0.005$) and recognition ($p < 0.05$) when compared to the control subjects (Figure 3.2). Thirty five per cent ($n=16$) of control subjects did not detect, and 74% ($n=32$) did not recognise the bitter taste (Chi-squared = 10.45, $p < 0.05$). In contrast, when compared to controls, a greater number of cancer patients detected and recognised bitter at the lowest concentration whereas only 18% cancer patients ($n=10$) did not recognise bitter and 9% ($n=5$) did not detect the bitter taste.

In this study, the majority of control subjects detected and recognised salt either at the highest concentrations or not at any level (Figure 3.3). The salt recognition profiles for

cancer patients reflected a similar threshold pattern. This suggests no difference in the ability of cancer patients and control subjects to recognise salt taste. However, the detection of salt was remarkably higher in the cancer group when compared to controls ($p<0.05$, Figure 3.3).

Concerning sour taste modality, the group of cancer patients exhibited a significantly lower threshold for sour detection ($p<0.05$) when compared to the control subjects. There were no differences between the groups in the recognition of sour taste (Figure 3.4).

For the detection of sweet perception, no significant differences were noted between the detection and recognition thresholds of the cancer and control groups (Figure 3.5).

Based on the above information, the null hypothesis (1) is rejected and the following hypotheses are accepted:

Patients with advanced cancer exhibit significantly lower gustatory detection thresholds for bitter, salt and sour tastes compared to age-matched control subjects.

Patients with advanced cancer exhibit significantly lower gustatory recognition thresholds for bitter taste compared to age-matched control subjects.

3.2.3 Olfactory perception

In this study the relationship between the chemosenses, gustation and olfaction was assessed. To assess olfactory perception, patients were asked to identify samples of 10 common odours from which scores were attributed to the number of odours correctly identified. For example, a score of 5 out of 10 indicated that 5 out of 10 samples were correctly identified.

The number of odours identified by cancer patients were significantly higher than that of control patients ($p < 0.05$). Median number of odours identified by cancer patients was 5 (Inter-quartile range 1.8) and for controls was 2 (Inter-quartile range 1.6, $p < 0.001$). The majority of control patients (90%) identified between 1 and 4 odours whereas 95% of cancer patients identified between 3 and 8 samples (Figure 3.6).

Based on these results, the null hypothesis (2) is rejected and the following hypothesis is accepted:

Patient with advanced cancer exhibit significantly lower olfactory thresholds compared to age-matched control subjects.

3.2.4 Reporting of olfactory and gustatory changes

The subjective reporting of any altered gustatory and olfactory perception were recorded using 2 open ended questions (see appendix 6). This data was used to compare the impact of altered gustatory perception on outcome measures such as QOL assessment, dietary

intake and food selection. In addition, subjective changes were compared with objective gustatory and olfactory assessments.

None of the control subjects reported any recent or previous alteration in gustatory perception. Neither a loss of taste or specific taste changes were noted within the control group. In addition, current or recent changes in olfactory perception were not evident in any of the control subjects.

Almost three quarters of patients with cancer (n 41; 73%) reported experiencing altered taste perception during the course of their malignant disease (Table 3.5). Of these cancer patients, 68% (28 out of 41) associated changes in taste perception with a loss of olfactory perception. The cancer patients also noted enhanced changes in taste perception. Ten patients (18%) reported an increase in bitter taste of food and 6 patients reported enhanced sweet perception (Chi-squared = 4.92, $p < 0.05$).

Fourteen patients (34%) first noticed gustatory changes at diagnosis. However, for additional 14 patients (34%), the onset of taste aberrations was more recently noticed, within a few weeks prior to questioning. Approximately half of all of the cancer patients had received previous chemotherapy or radiotherapy as part of treatment, but not less than 3 months before inclusion in the study. However, only 5 patients (18%) associated the onset of taste changes with any previous periods of radiotherapy or chemotherapy.

For patients reporting noticeable taste changes, approximately half (53%) reported experiencing a continuous change in taste perception. In addition, 14% described changes

in taste perception as at times less noticeable and 14% as at times improving. The prevalence of taste aberrations was examined when patients were stratified by primary tumour diagnosis. Table 3.6 highlights the reporting of taste changes in patients with a variety of tumour diagnoses. The majority of patients within each tumour sub-group reported altered taste perception. Within this heterogeneous group, 60% (n=18) patients with metastatic disease reported changes in taste perception.

The association between objectively measured changes using the dilution test and reported taste thresholds of cancer patients was determined. Associations between the subjective and objective assessments of taste perception were noted with respect to bitter and sweet tastes. All subjects who reported a noticeable increase in bitter taste perception (n=10) detected bitter at levels 1-4, of whom 8 recognised the taste of bitter. Likewise, 80% of patients who reported an increase in sweet perception (4 out of 6), whereas only 20% of subjects who did not report this phenomenon, recognised sweet at the lowest 2 concentrations (Chi-squared = 4.95, $p<0.05$).

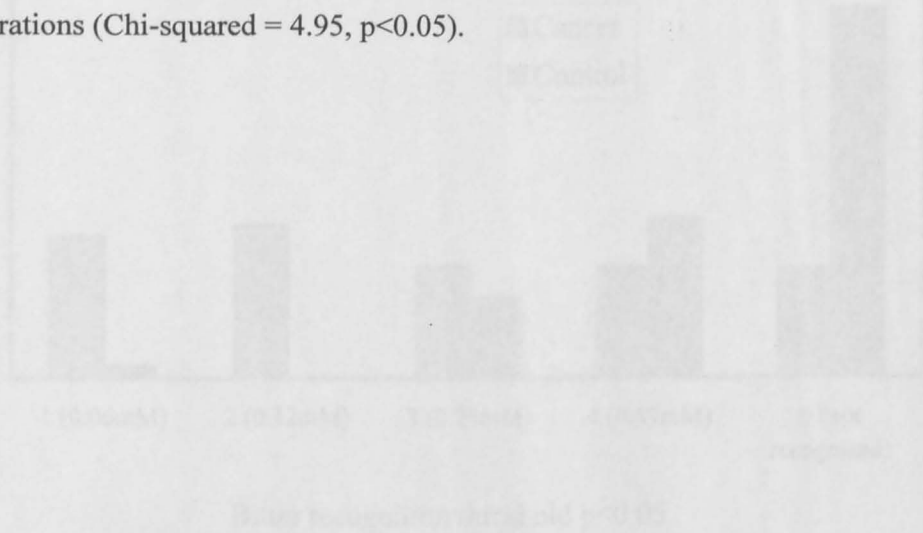


Figure 3.2: Taste perception profiles (bitter and sweet) of cancer patients and control subjects

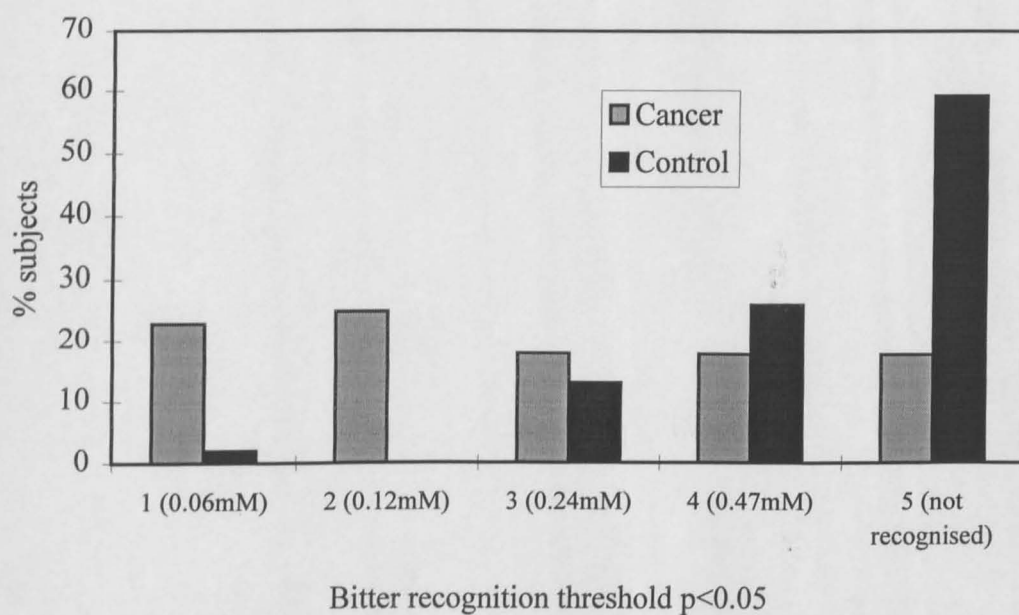
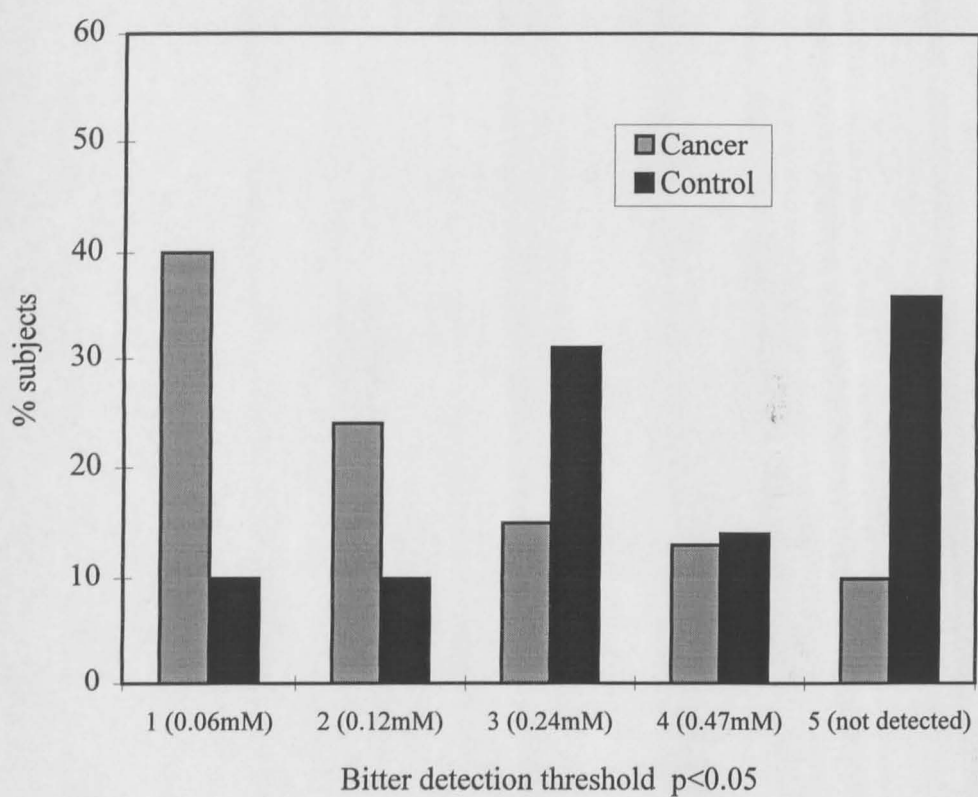


Figure 3.2 Comparison of bitter taste profiles (caffeine) of cancer patients and control subjects

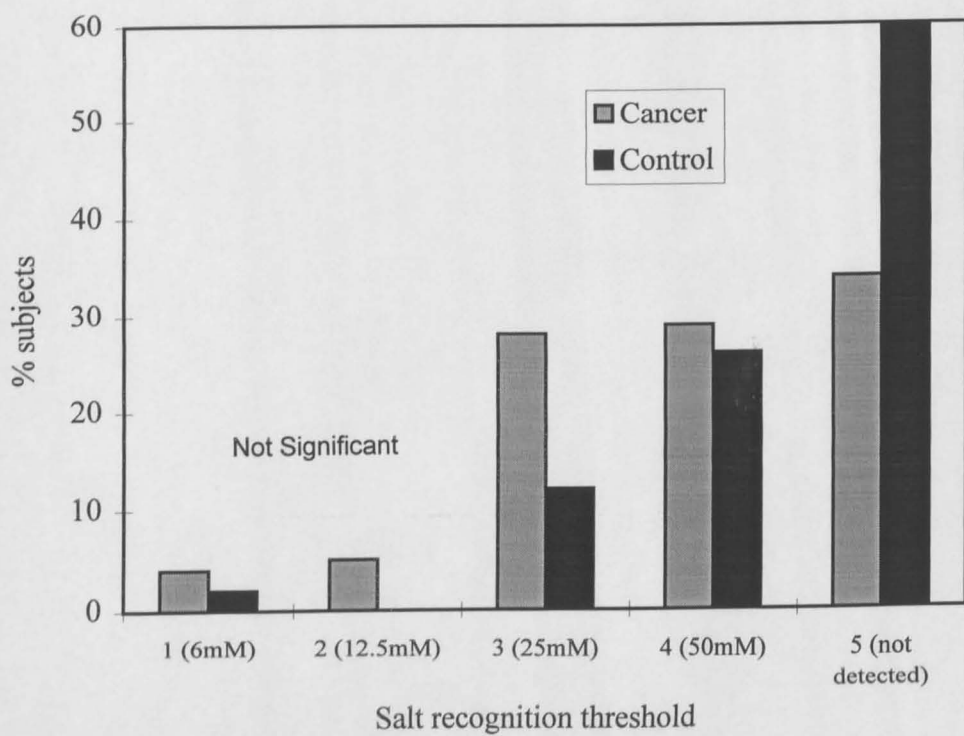
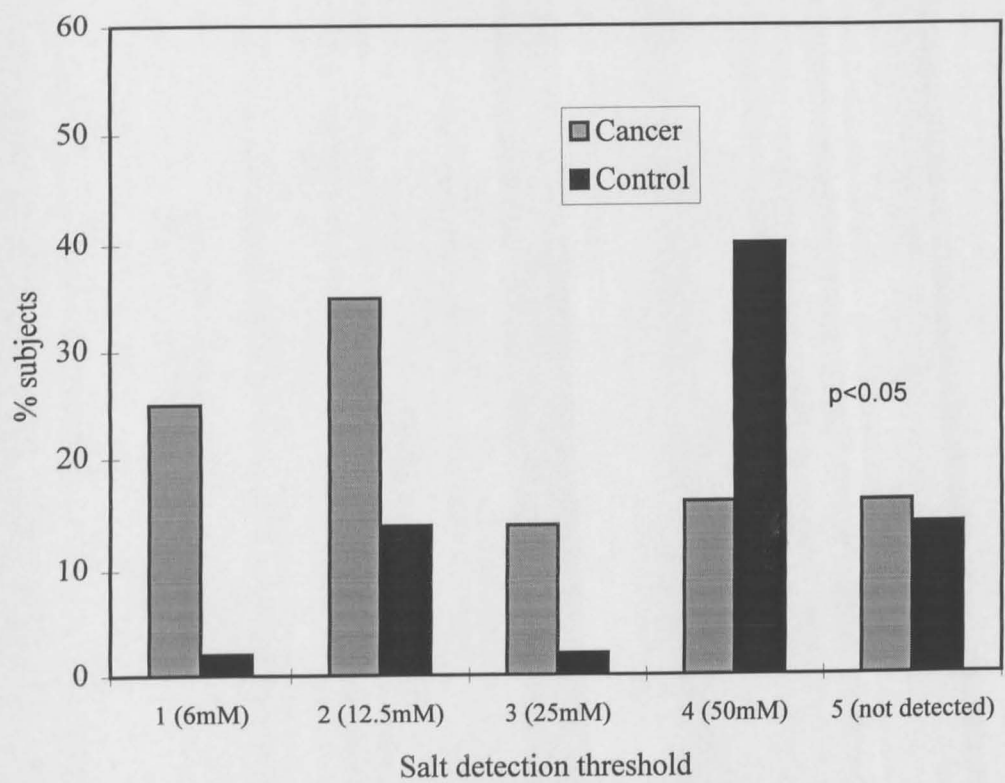
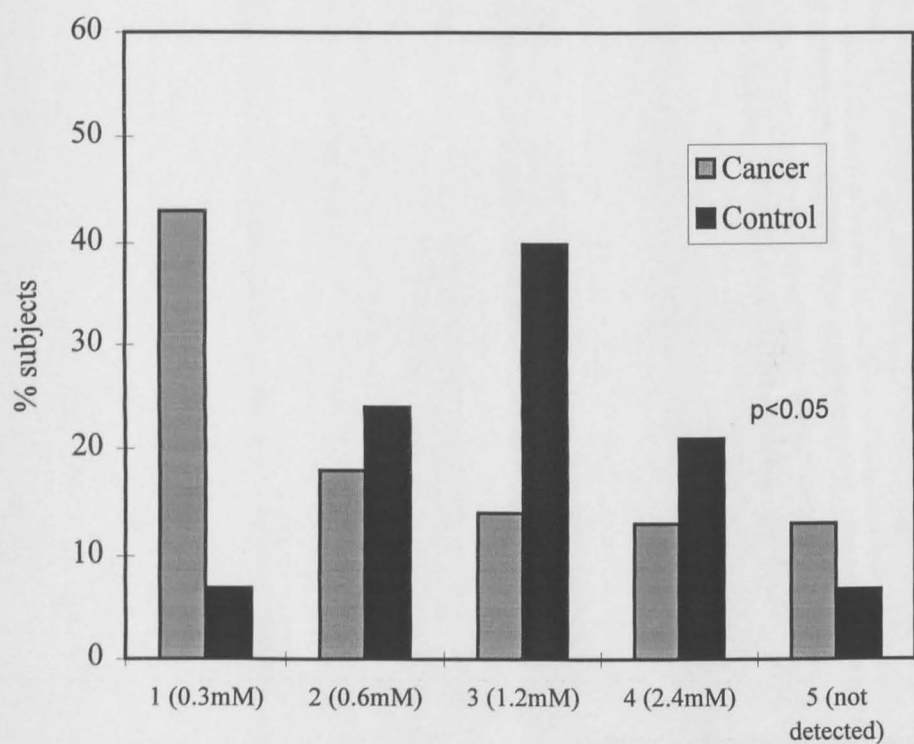
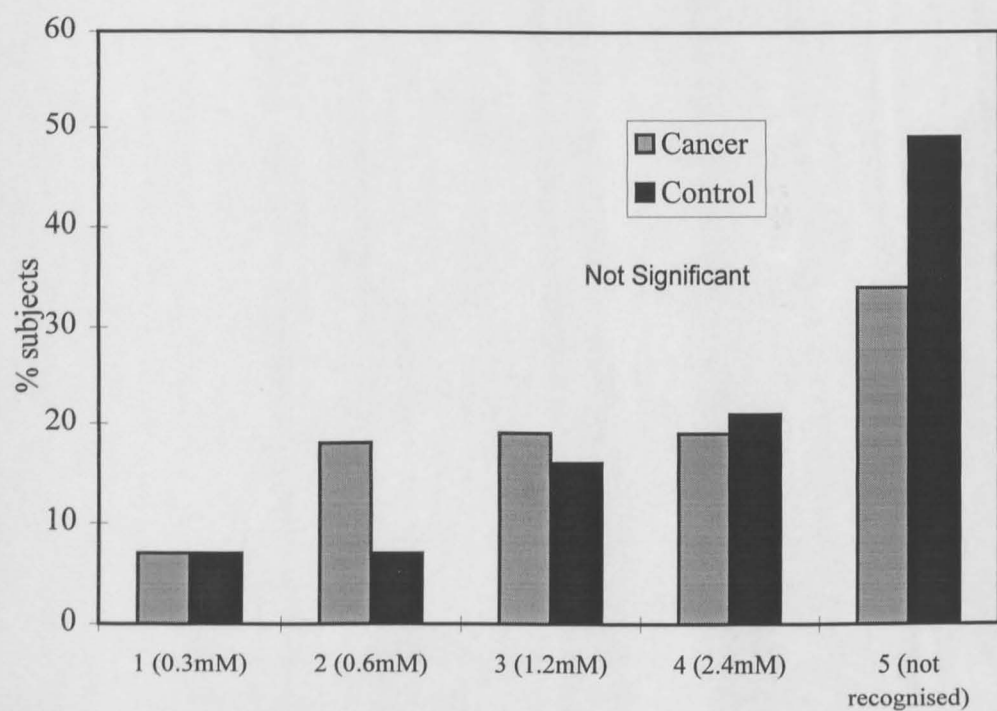


Figure 3.3 Comparison of salt (sodium chloride) taste profiles of cancer patients and control subjects



Sour detection threshold $p < 0.05$



Sour recognition thresholds

Figure 3.4 Comparison of sour (citric acid) taste profiles of cancer patients and control subjects

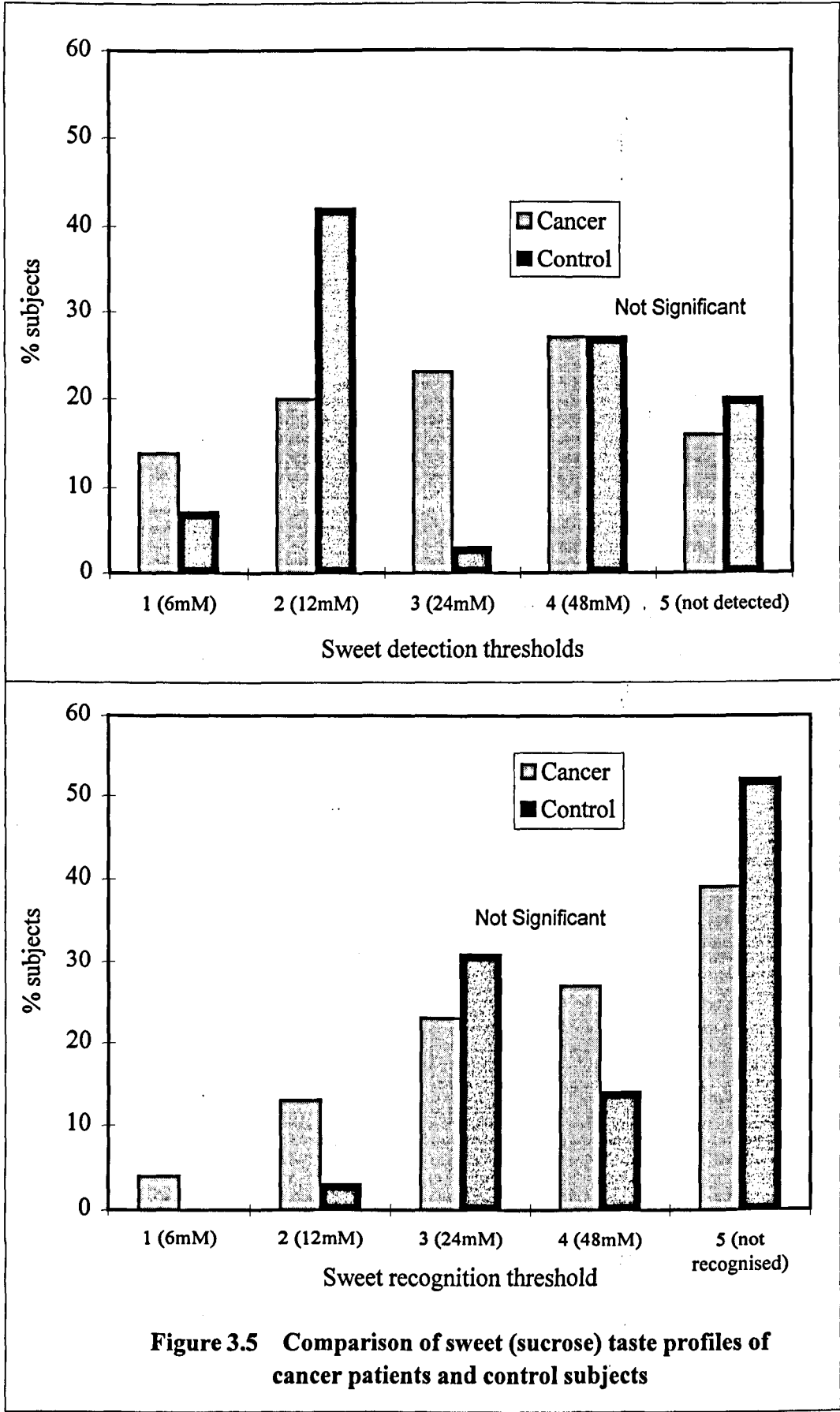


Table 3.3 Description of changes in taste perception by patients with cancer

Description of gustatory changes	Cancer patients	
	n	%
Loss of taste (blunting of sensitivity)	19	34
Enhanced bitter perception	10	18
Enhanced sweet perception	6	11
Enhanced salt perception	3	5
Unspecified taste aberration	3	5
No change in taste perception	15	27

Table 3.4 Prevalence of altered taste perception stratified by primary tumour

Primary Tumour Location	Patients who reported an alteration in taste perception n=41		
	n	% patient reporting changes	% tumour group
Bowel	10	24	67
Breast	9	22	75
Ovary	5	12	83
Prostate	2	5	67
Lung	2	5	50
Kidney	1	3	50
Unknown	2	5	100
Other	10	24	83

3.2.5 Drug regimens of patients with advanced cancer

A total of 63 different types of medications were prescribed for patients with advanced cancer. To facilitate interpretation, these generic drugs highlighted in table 3.7, have been grouped by indication. Of these patients, ten had received more than one type of analgesic during participation in the study.

Medications were examined in relation to both subjective reporting of taste changes and the objective determination of taste profiles. Following chi-squared analysis, medication regimens indicate no differences in the number of drugs taken by patients stratified by subjective taste perception (Figure 3.7 and Table 3.8). Similar patterns of prescribed medications may be seen with all sets of patients. In addition, medication regimens amongst those patients who detected and recognised bitter and sweet tastes were also examined (table 3.9). No differences between groups were reflected in the taste profiles.

Table 3.5 Medication prescribed for patients with advanced cancer

Indication	n	% total group (n=56)
Analgesic	52	93
Anti-emetic	16	29
Laxative	29	52
Anti-diarrhoeal	3	5
Steroids	16	29
Diuretic	9	16
Sedative	32	57

Table 3.6 Medication stratified by reporting of taste changes

Indication	Taste changes reported n=41	No taste changes reported n=15
	n (%)	n (%)
Analgesic	41 (100)	13 (80)
Anti-emetic	8 (20)	7 (47)
Sedative	38 (93)	12 (73)
Laxative	20 (49)	8 (60)
Anti-diarrhoea	2 (5)	1 (7)
Steroids	10 (24)	6 (40)
Diuretic	5 (12)	2 (27)

Table 3.9 Medication stratified by bitter taste perception

	Bitter detected (thresholds 1-4) n=51		Bitter not detected at any level n=5	
	n	%	n	%
Analgesic	31	92	4	75
Nausea	11	32	2	40
Laxative	20	59	2	40
Anti diarrhoea	3	9	0	0
Steroids	9	26	2	40
Diuretic	5	15	0	0
Sedative	27	79	4	88

	Bitter recognised n=46 (threshold 1-4)		Bitter not recognised at any level n=10	
	n	%	n	%
Analgesic	19	95	10	100
Nausea	7	35	4	36
Laxative	8	40	6	55
Anti diarrhoea	3	15	0	0
Steroids	3	15	9	50
Diuretic	4	20	1	10
Sedative	15	75	4	41

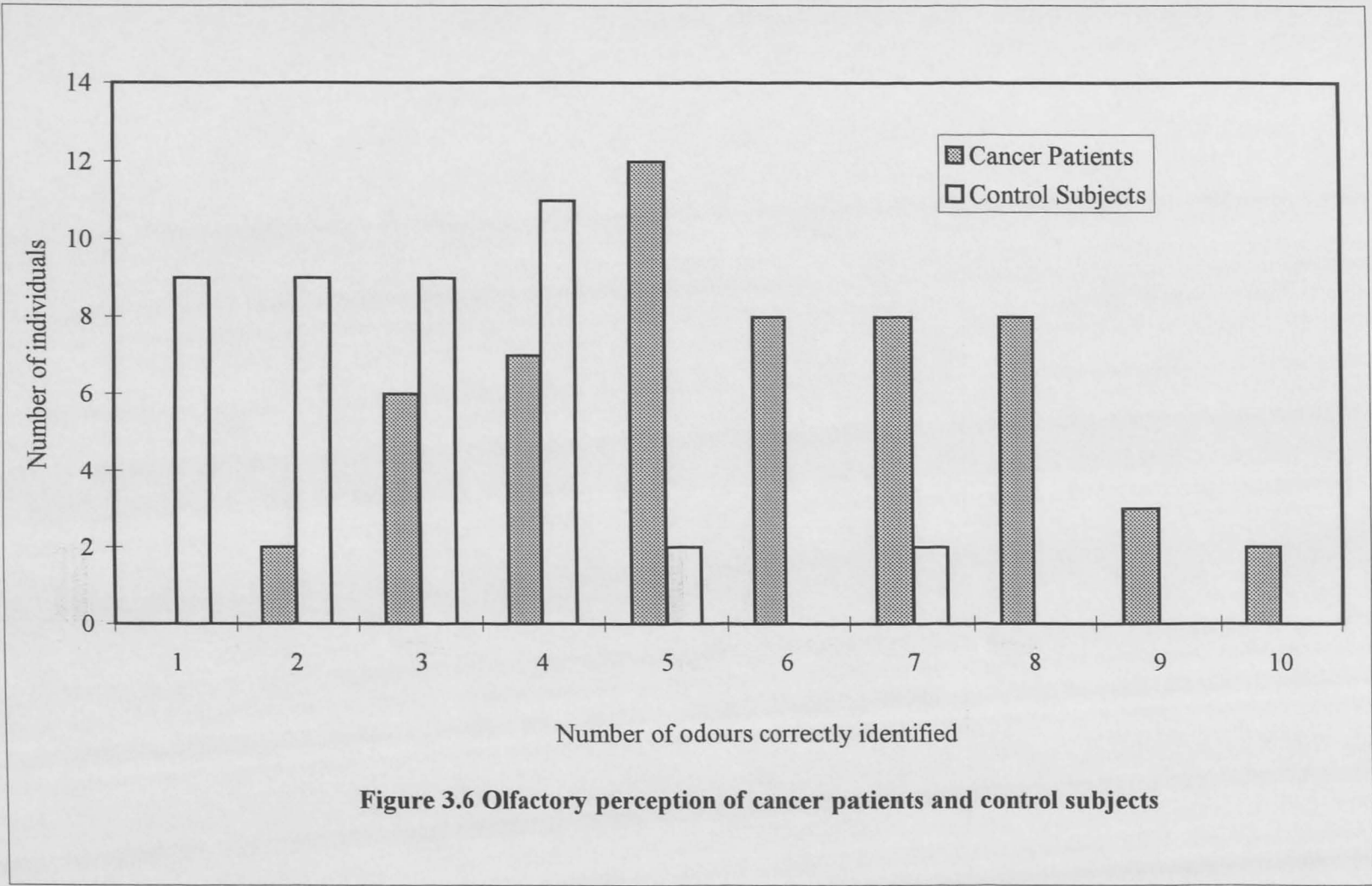
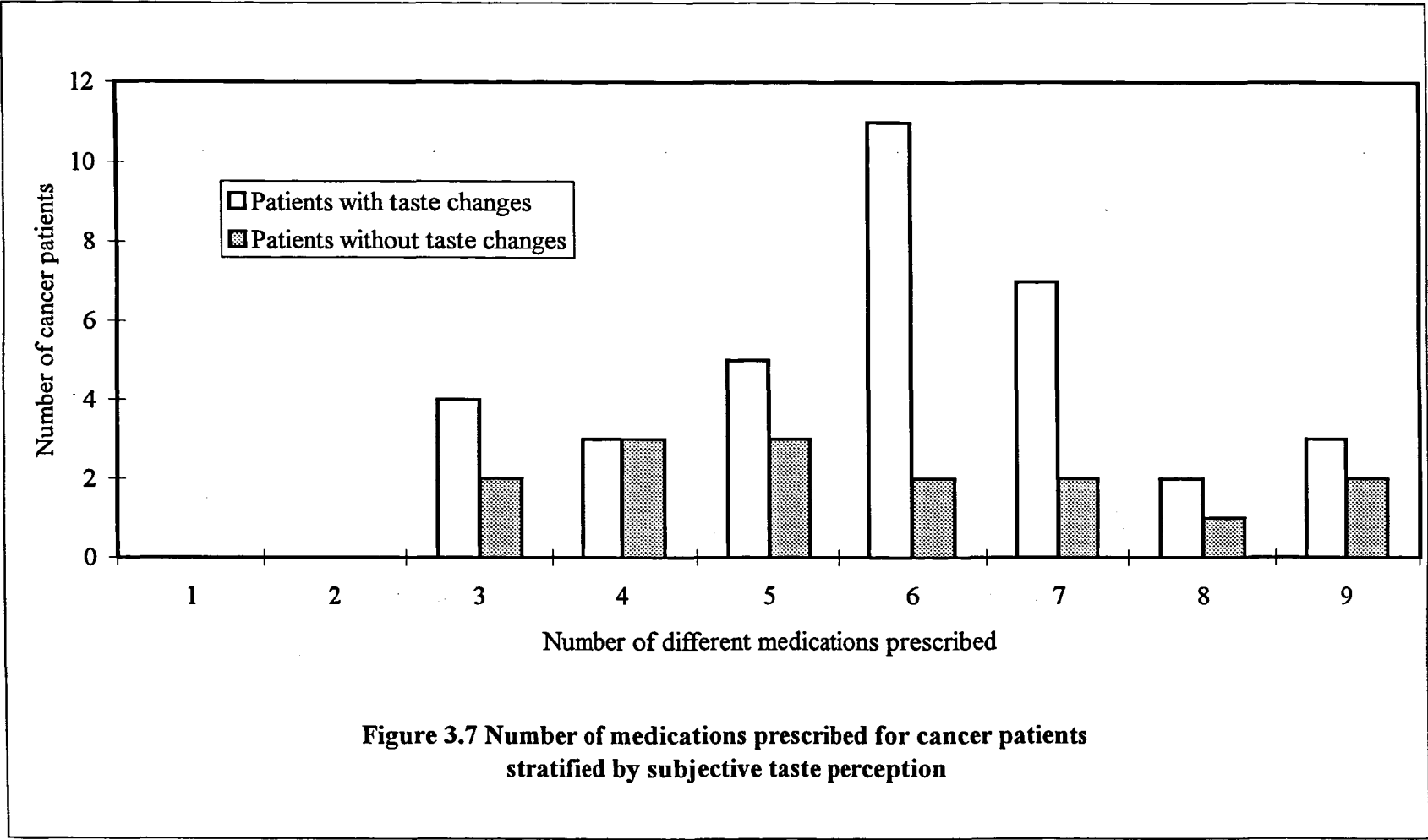


Figure 3.6 Olfactory perception of cancer patients and control subjects



3.3 Discussion

3.3.1 Recruitment

Patients with advanced cancer

Within this cohort, 56 patients successfully completed the study assessments and an additional 18 patients, who did not complete all of the assessments, withdrew due to a deteriorating medical condition. Although, the majority of patients were recruited following adequate symptom control, this drop-out rate of 24% highlights that recruitment and retention of patients receiving palliative care in this study was difficult mainly due to changing medical condition. In an attempt to maximise recruitment, clinical research of this nature involved time in screening patients, a procedure which involved attending the medical and nursing ward rounds and increasing awareness of all staff of the study inclusion criteria through regular training sessions. Study progress and results were disseminated at meetings with medical and nursing staff.

It was acknowledged that rigorous exclusion criteria might impinge on the number of subjects recruited and possibly introduce selection bias that may limit the interpretation of the results. No specific cancer types were excluded from the study.

A variety of primary tumour diagnoses were noted within this group of elderly cancer patients. The tumour type in this heterogeneous group reflects the main classification of primary diagnosis observed in the UK epidemiological picture (WHO Classification,

1983). The main tumour diagnosis for males was lung cancer and for women breast cancer. In an advanced stage of their illness, the majority of subjects (67%) had metastatic disease but the time available did not allow for a greater number of patients recruited to this study to examine taste profiles in relation to specific tumour type. Despite the heterogeneous nature of these patients, this study has focused on patients with an advanced stage of disease receiving palliative care who have not received any recent radiotherapy or chemotherapy. This is the first study of its kind and the following results uniquely contribute to the knowledge and understanding of taste perception not attributable to aggressive treatment regimens in patients with advanced cancer.

Control Patients

The predominance of females recruited in the majority of studies of elderly populations was reflected in this current study within both the control subjects (57% female) and cancer patients (73% female) (Schiffman, 1994).

The sample of elderly subjects recruited from the Geriatric Assessment Unit were appropriately matched controls for several reasons. Firstly, this group were of similar age as that of the cancer patients and none had evidence of neoplastic disease or an ongoing inflammatory response. None of the patients were acutely ill as confirmed by serum C-RP levels. In addition, patients were assessed prior to discharge. Secondly, with regard to taste perception, the pilot study demonstrated higher thresholds for all four tastes in the control elderly group when compared to a younger group of subjects. In this study, a blunting of taste perception noted in the control subjects supports the recent work of

Schiffman (1997) who demonstrated a deteriorating taste sensitivity with age. This is important in controlling for the effects of age on normal taste bud physiology in the cancer group whose mean age was similar to that of the controls subjects (Weiffenbach *et al*, 1986; Hill and Almi, 1980). In addition, the analysis of the taste profiles of the controls and younger counterparts suggests that the chosen gustatory assessment tool had the ability to detect expected differences in taste profiles. This is important data as it validates the use of 4 rather than 6 concentrations in the adapted sensory appraisal test.

3.3.2 Prevalence of altered taste perception in patients with advanced cancer

Establishing the taste profiles of control subjects was fundamental to the study in order to subsequently compare with profiles of the cancer patients. Although not significantly different, taste profiles indicate that the control subjects exhibited a blunting of taste perception as compared to their younger counterparts and hence demonstrate changes in taste perception attributed to the ageing process. In this study, more than half of patients with advanced cancer reported an alteration in their taste perception during the course of their illness. For the majority of these patients, gustatory changes were reported as a blunting of taste perception coincident with ageing. It may also be characteristic of nutritional deficiency associated with advanced cancer which will be discussed in chapter 6. Although, no specific taste changes were noted in control subjects, Duffy and colleagues (1995) noted a lower sensitivity for bitter and sour taste in a healthy elderly population. However, specific changes in taste perception were also observed in the cancer group. More than one third of patients reported an increase in bitter taste perception and others reported a heightened sensitivity to salt and sweet tastes. For some patients, an

increased sensitivity to bitter accompanied a general blunting of taste. In contrast, none of the control patients reported any changes in gustatory and olfactory perception. This study uniquely highlights specific and predominant changes in taste perception not attributed to cancer treatments such as radiotherapy and chemotherapy. Moreover, patients did not associate the onset of gustatory and olfactory changes with any previous treatment. This suggests that chemosensory changes are not evident as a side effect of treatment but may be attributed to the malignant disease process.

Apart from the malignant state in the cancer patients, there may be other differences from the control group that would attribute to differences noted with gustatory and olfactory perceptions. Other known conditions include chronic liver disease (Madden et al, 1997) and nutritional deficiencies (Schiffman, 1991). None of the control patients had evidence of liver disease. Although antropometric and assessments of dietary intake revealed no overt nutritional deficiencies within the control group, no biochemical assessment was performed to detect any sub-clinical under-nutrition. In addition, obesity has been associated with heightened hedonic responses to fat containing stimuli (Drewnowski et al, 1985). However, no evidence of obesity was evident within either group.

Only 3 out of 35 patients questioned were unable to precisely attribute the change in taste perception to one of the 4 primary tastes (sweet, sour, salt or bitter). These patients associated their alteration in taste perception with a particular food item for example, an increase in sweet perception was described 'as though an extra spoonful of sugar has been added'. Responses were often very descriptive where a blunting of taste perception was described as 'food just tastes like cotton wool'. Previously, Mott and Leopold (1991)

reported that as many as 13 out of 50 patients could not accurately classify taste disturbances. Food items are a composite of taste and smell and it may therefore be difficult to distinguish between specific tastes.

The prevalence of altered taste perception in this present study was higher than that previously reported by DeWys and colleagues (1974) who observed this symptom in more than half of a group of 50 heterogeneous cancer patients. Likewise, approximately half of patients in a hospice setting studied by Walsh and colleagues in 1982 were experiencing gustatory changes. However, the heterogeneous group of patients with advanced cancer studied by Walsh included patients who had received recent radiotherapy or chemotherapy which is known to cause a blunting of taste sensation (Conger 1973, Beidler and Smith 1991, McDaniel *et al*, 1995). It is interesting that in the current study, which included patients who had not received any recent treatment, that the prevalence of altered taste perception is greater than that noted by Walsh and colleagues. It must be recognised that, methodological differences may play a part in the non-homogeneity of findings in the determination of taste profiles. One such difference lies in the various sensory appraisal techniques used such as the 'forced choice' technique (Henkin, 1963) and the 'up-down' technique (Bartoshuk, 1978). Many studies in cancer patients have included patients who have received medication that may influence taste perception such as Nystatin for treatment of oral thrush. This methodological difference may also in part explain differences in taste perception studies with certain disease states including cancer studies. This is particularly relevant to cancer patients who have received active chemotherapeutic agents or radiotherapy treatment, which may directly alter taste bud physiology.

Medication regimens and altered taste perception

Previous studies have reported that specific medications such as Nystatin for oral thrush may affect taste perception. To examine the causes of alteration in taste perception noted in this study, the pharmaceutical regimen of all recruited cancer patients were documented. None of the patients were receiving any medications that are known to influence taste perception. Although, in many cases, patients were prescribed a number of medications for symptom control, there appeared to be no pattern in either the number or type of medications.

With particular reference to bitter perception, there was no difference in the type of medication for patients with heightened sensitivity as compared to the remaining patients. The effects on taste perception of the duration or cumulative dosage or medication that patients were receiving remains an area of interest for future studies.

3.3.3 Taste perception profiles

When comparing the objectively measured taste thresholds for the four primary tastes, significant differences were highlighted between taste thresholds of the cancer patients and control subjects. Each of the four taste qualities of sweet, sour, salt and bitter will now be discussed. In addition, patterns of taste aberrations in relation to olfactory perception and reported taste perception are highlighted.

Salt perception

For the detection of salt, patients with advanced cancer demonstrated heightened salt detection when compared to the control subjects. In other words, salt was detected significantly earlier in the cancer group compared to the controls. Carson and Gormican (1977) have previously reported significantly higher thresholds for salt taste in a group of patients with breast and colon cancer. However, the majority of studies in this area have not demonstrated an alteration in this taste modality in cancer patients. In this current study, it is difficult to explain the reasons for heightened salt detection coupled with a suppressed salt recognition in cancer patients. It may be suggested that differences in salt detection reflect difficulties in recognising salt perception whereas the detection of a taste requires no decoding of stimulant. However, when extrapolating these results into the selection of food items, detection thresholds may be important in determining food selection although there is little evidence for thresholds alone to be related to food selection. Alternatively, an elevated salt threshold has been associated with an increased concentration of sodium ions in saliva production (McBurney and Pfaffman, 1963). The chemical nature of salt perception involves translocation of salt taste into the receptor cell through passive movement of sodium ions through the apical channels innervated by the chorda tympani (Spector and Grill, 1992). In this current study, assessment of saliva was considered invasive in terminally ill patients. Anecdotally, a dry mouth indicative of reduced saliva production, was not associated with an alteration in taste perception by any cancer patients.

Sweet Perception

Differences in the detection of sweet taste between the cancer patients and control subjects

were noted. Within both groups, more than half of individuals did not recognise sweet perception at any level. Likewise, few individuals detected sweet taste. This highlights either a blunting of sweet perception in both cancer patients and control subjects or suggests that the test stimuli were too weak. Although not reflected in objectively measured profiles, an increase in sweet perception was reported by 17% of cancer patients compared to none of the control group. The reasons for this inconsistency are unclear but may be due to differential signalling mechanisms related to sweet perception.

Bitter Taste Perception

The most notable comparison between cancer patients and controls was in the detection and recognition of bitter taste. Patients with advanced cancer exhibited significantly lower thresholds for bitter taste compared to controls. This finding has not previously been reported in patients with advanced cancer receiving only palliative care. Previous research has found an increase in threshold for bitter and sour in cancer patients receiving treatment (Carson and Gormican, 1977). Within other homogeneous tumour types which have included patients receiving treatment, elevated bitter taste sensitivity has been noted (DeWys and Walters, 1975; Williams and Cohen, 1978; Settle *et al*, 1979; Hall *et al*, 1980). In these studies, the effects of treatment regimens shadow the impact of the disease process on taste perception.

When taste perception profiles of the cancer group were stratified by tumour histology, patients with breast and bowel cancers had a greater sensitivity for bitter taste perception. This may have merely reflected the number of patients recruited in each of these two

tumour types. However, part of this explanation may lie in the fact that 50% of breast cancer and 88% of colon cancer patients had lost weight and 82% exhibited metastatic disease. This is indeed important considering that weight loss has previously been associated with higher taste thresholds (Ovesen *et al*, 1991). However, the group studied by Ovesen was limited to that of small cell lung cancer who were receiving treatment. These results suggest that metabolic effects of these 'solid' tumours influence bitter taste more readily than other primary tastes. In this current study, approximately three quarters of patients had known metastatic disease. Of these, 60% of subjects with metastatic disease reported experiencing altered taste perception.

Settle and colleagues (1979) observed a significantly higher recognition thresholds for all tastes in subjects with metastatic disease compared to healthy controls. This suggests that taste aberrations are influenced by tumour site. Different sited tumours are associated with specific metabolic effects. For example pancreatic tumours are associated with rapid weight loss and breast cancer with minimal amounts of weight loss. This may in some way explain the differences but metabolic effects will be discussed more thoroughly in chapter 7. It may be argued that difference in methodologies adopted and patient populations may explain these inconsistencies.

Mechanisms of bitter taste appear to be the most complex in terms of transduction mechanisms. Alterations at the transduction level may explain why heightened bitter taste profiles were only evident in these patients with advanced cancer. The mechanisms of which may be related to metabolic effects of the tumour or the host response to the tumour.

Sour detection thresholds of cancer patients were significantly lower than that of the control subjects. This suggests that the cancer group had the ability to detect sour at a lower concentration. No differences were noted in the sour recognition profiles of these two groups. Shifts in sour perception may be associated with heightened bitter taste perception due to difficulties in distinguishing between these two modalities. At a cellular level, both sour and bitter taste perceptions are mediated by K^+ channels, which regulate the depolarisation of the taste cell and the subsequent activation of neurotransmitter release. Based on this information, a change in sour and bitter taste as demonstrated in this current study, may simultaneously occur as part of the taste perception neural processes.

It is important to review the results with caution. Within both groups, there is potential for cognitive bias, that is, subjects report what they believe or want to be correct (Mela and Rogers, 1998). This may be particularly so with cancer patients who may assign a higher threshold to a stimulus that they like but is associated with previous treatment.

3.3.4 Olfactory perception

When considering changes in gustatory perception, the association with olfactory perception must be addressed as both chemosenses are important determinants of food selection and hence dietary intake in healthy adults (Bernstein, 1994). It is important to note that the patients and controls were screened using the abbreviated mental test to include patient with an adequate memory. This reduced the error in identifying odours due to memory loss.

In this study, comparisons were made between the objective markers of gustatory and olfactory chemoreception. Results reveal that the control subjects identified fewer odours when compared to the cancer patients indicating a general heightened olfactory perception in advanced cancer, which suggests a close interplay between gustatory and olfactory chemosenses as there are in healthy people. Further investigation revealed that patients with heightened bitter taste perception also exhibited heightened smell perception. This suggests that the mechanism of altered gustatory perception occur at the same time as olfactory perception. As with gustation, no control subjects experienced changes in self-reported olfactory perception. The association between gustatory and olfactory chemosenses in advanced cancer has not previously been reported and together may be important in the development of food aversions and altered satiety mechanisms, a knowledge of which is crucial in the appropriate management of nutritional support in this population. Attempts to minimise the impact of odours in food preparation methods might improve the impact of sensory influences on food selection and dietary intake. This factor may be important in product development of nutritional supplements for example strawberry odour may not smell as fresh strawberries to patients.

3.3.5 Subjective taste reporting

The relationship between the subjective reporting of taste changes and the objectively measured taste profiles are important for two main reasons. Firstly, if the objective research tool is used as the basis of intervention, it must mirror what the individual reports. When considering management of this symptom, the objectively measured profiles will

prove important in determining the efficacy of any subsequent nutritional intervention. Secondly, subjective reporting reflected in objective assessment indicates that the objective tool accurately assesses taste perception.

For bitter taste, results indicate that all patients who reported heightened sensitivity to bitter taste, recognised bitter at the lowest concentrations. These results provide further justification for using the chosen objective tool. DeWys and colleagues (1974) previously reported a correlation between subjective and objective taste perception in cancer patients. However, in other clinical states for example, liver cirrhosis, no correlation was noted between subjective and objective assessments of taste perception (Madden et al, 1997).

In this study, the technique for measuring taste perception was similar to that used in this current study. For example, responses of bitter detection were divided into either 'yes' indicating that bitter was objectively detected or 'no' indicating that bitter was not detected at any level assessed. A similar scoring strategy was adopted in this current study to reveal an association between the subjective reporting of taste changes and the detection and recognition of bitter taste. All ten patients who reported an increase in bitter taste perception, detected bitter and 8 recognised the taste of bitter using the objective assessment technique.

It is foreseeable that in certain cases there may be no correlation between objective and subjective taste perceptions. The reasons for this may be twofold; firstly, as highlighted by Kamath and Booth in 1983, the perception of aqueous solutions may not be accurately translated into the perception of food items in which compounds of several tastes are

present. Also subjective taste reporting involves not only concentration effects but also tactile senses. Secondly, the emphasis that patients with advanced cancer place on nutritional symptoms and the experience of altered taste perception may be overshadowed by more predominant symptoms such as pain and fatigue. In contrast, the awareness of symptoms associated with the disease process may heighten patients' awareness of any changes in taste aberrations.

For each primary taste, detection and recognition thresholds were noted at different concentrations. The physiological principles underlying detection and recognition perceptions differ and this in part may explain differences in the concentrations at which tastes are detected and recognised. Shepherd (1991) describes the first operation in sensory transduction (encoding of a stimulus into an electrical response) as detection of sensitivity of a taste, followed by recognition of a stimulus. This may in part explain the intra-subject differences in the detection and recognition of a stimulus. Neuronal processing of recognition may be different to those of transduction and therefore affected differently in disease states.

From results obtained and comparison with published data, the use of four compared to the standard six solutions was appropriate for both the control and cancer group of patients. For all four tastes, a number of cancer patients detected the taste within the range of concentrations. The use of four solutions however does reflect the difference in thresholds between the two groups and avoids the use of a lengthy assessment tool. However, for patients who detected tastes at the lowest concentration, the precise detection threshold needs to be further explored using a wider range of solutions of weaker concentrations. In

addition, a subjective element is present in the interpretation of taste perception by the patient was acknowledged. In this current study, solution concentrations and techniques of assessment such as the time of day that the test was performed and the assessment environment were standardised.

3.3.6 Summary

The most notable pattern emerging in this study of patients with advanced cancer is that of a heightened bitter taste perception. The possible causes of the altered bitter taste perception are further examined in chapter 7. These results have previously been demonstrated in cancer patients but not in a group of patients with terminal advanced cancer receiving palliative care only. This study suggests that these patients demonstrate different patterns of taste perception compared to patients receiving active treatment or medication that may influence taste perception. In addition, the patients with advanced cancer demonstrated heightened olfactory perception as compared to age matched controls. These results are important in terms of the impact on the management of symptoms associated with malignancy, of which symptom control is fundamental to the maintenance of QOL of patients.

4.1 Introduction

Null Hypothesis (3) There is no relationship between gustatory perception and quality of life in patients with advanced cancer.

Fifty patients with advanced cancer completed the semi-structured interview based on the HAD scale (Appendix 6). This examined firstly, the impact of altered taste perception on QOL and secondly an assessment of some general aspects of QOL (Table 4.1 and 4.2). The assessment of QOL, a subjective outcome measure, is considered in relation to the subjective reporting of changes in taste perception. This assessment contextualised the impact of taste aberrations on QOL, in terms of the enjoyment of food and changes in food selection. Examples of responses given by patients to each question are reported in this chapter to illustrate any impact that altered taste perception may have on QOL.

4.2 Results

4.2.1 Have the taste changes affected your eating habits?

Almost half of the patients reporting taste changes (n=16, 46%), attributed a reduction in dietary intake to a change in taste perception. Only one patient reported that their dietary intake increased due to altered taste perception. In addition, 40% patients (n=14) consequently reported a change in food selection resulting from altered taste perception. Changes in food selection are further explored in chapter 6. This data suggests that for some patients, altered taste perception had an impact on not only the amount of food

consumed but also the type of food selected.

"I eat different ready-made meals now because all food taste the same"

(70 year Female, Colonic cancer with liver metastases)

"I love baton buns with strawberry jam but it tastes like cotton wool"

(75 year Male, Gastric cancer)

"I do eat different foods now. I often want something tasty but I have an extra problem that at home I do not feel well enough to cook"

(75 year Female, Ovarian cancer)

4.2.2 Do you sometimes feel hungry but the taste puts you off?

The question 'Do you sometimes feel hungry but the taste puts you off?' explored the impact of altered taste perception on appetite. Of the group of cancer patients, 14% experienced early satiety (n=8). However, of the remainder, despite either occasional or frequent feelings of hunger, 40% (n=19) reported that an altered taste of food reduced their appetite. Although not statistically significant, for patients who did not experience early satiety, altered taste perception had a negative impact on their appetite.

"I frequently feel hungry at night but food often does not taste right"

(54 year Female, Breast cancer)

4.2.3 Have the taste changes affected your general enjoyment of life?

Of the 35 patients reporting taste changes, almost three quarters reported that the presence of altered taste perception affected their general enjoyment of life. This was described as a significant negative effect by 20% patients and as quite a lot by 24% patients. Although not statistically significant, for additional 24% patients, altered taste was noted as having

little effect on appetite.

“As a diabetic, diet has always affected my lifestyle and now my taste changes have an effect on my life”

(65 year Female, Breast cancer)

For other respondents, taste changes did not impinge on their QOL and were regarded as one of several symptoms associated with their illness:

“Taste changes have little effect of my life as it is just a minor part of what has been happening in relation to my disease”

(89 year Female, Breast cancer)

“Taste changes do not have any effect on my enjoyment of life that would put too much emphasis on the role that food plays in life”

(62 year Male, Prostate cancer)

4.2.4 Have the taste changes affected those close to you?

In relation to other aspects of everyday life, either family or friends noticed the presence of taste changes. Almost one third of patients (31%) described altered taste perception as a major worry for their carers. In addition, 17% reported that friends and/or family occasionally noticed this symptom. This question was not applicable for 17% patients who lived alone. More than three quarters patients reported that this concern was associated with a concern for weight loss and anorexia. The following responses by patients reflect some concerns of carers:

“My husband tries to please me by buying meringues but I just don't eat them”

(65 year Female, Breast cancer)

"Yes, it is a major worry for my family and when my family see me eating it is a victory"
(74 year, Female, Lung cancer)

"Taste changes are not noticed by my family, as I do the cooking for my wife as she is ill too"
(63 year, Male, Kidney cancer)

4.2.5 Do you ever feel too tired to eat?

This question was used to explore the impact of fatigue on the dietary intake in the group of cancer patients. Responses for both groups, that is, those who experienced taste changes and those who did not experience any changes. Tiredness was widely reported as a symptom that affected appetite (n=27). Although, not significant, tiredness was noted as more prevalent among patients with taste changes (n=19, 49%) compared to those patients who did not report any changes (32%).

4.2.6 Has your illness affected the interest you take in your appearance?

This question addressed the impact of weight loss and associated altered body image. Approximately, one third of all subjects (n=18) associated a lack of interest in their appearance with their illness. Of these patients, approximately 50% (n=8) also reported an altered taste perception. This data suggests that a reduction in appetite and dietary intake contributing to weight loss may have a negative effect on QOL.

"I rarely take an interest. When you are in pain you can't be bothered"
(74 year Female, Pancreatic cancer)

"No, I take the same interest in my appearance but I am concerned a great deal about my loss of weight"

(78 year, Female, Ovarian cancer)

4.2.7 How often do you socialise with your friends and family?

The majority of patients (70%) enjoyed sociable activities. Chi-squared analysis revealed no association between the presence of taste changes and socialising. The majority of patients either experiencing taste changes (67%) or not (80%) enjoyed socialising with family and friends.

4.2.8 Do you enjoy watching the television, listening to the radio or reading a newspaper?

With regard to these pastimes, almost half of all patients frequently enjoyed watching television, listening to the radio or reading a newspaper. For patients who were experiencing taste changes, one third (30%) reported that a lack of concentration reduced their participation in any of these activities, whereas this only applied to 6% who did not notice any altered taste perception (Chi-squared = 7.99, $p < 0.01$).

"Some days I enjoy watching television, but I often find it difficult to concentrate on television"

(67 year, Female, Ovarian cancer)

4.2.9 Do you have a hobby? Do you still enjoy it?

Approximately half of all patients felt unable to maintain any previous hobbies due to a lack of energy. This applied to both patients with or without any disturbances of taste perception.

4.2.10 Do you ever feel tense and nervous?

More than half of patients with taste changes reported that they felt tense and nervous either quite often or most of the time. This compares to one third (35%) patients who did not experience any taste changes (Chi-squared = 22.5, $p < 0.001$).

"I'm always highly strung but this has settled now while being in this hospice"
(89 year female, rectal cancer)

"Very rarely, only when my son questions why I don't eat well"
(76 year female, rectal cancer)

"I get tense quite often and worry about my condition"
(63 year male, kidney cancer)

"Get tense quite often, I admit that I've always been a bit of a worrier, mainly about money and bills"
(75 year, female, ovarian cancer)

4.2.11 Summary

It would appear that there are differences in the quality of life parameters between the patients with advanced cancer and control subjects. Therefore the null hypothesis (3) is rejected and the following hypothesis is accepted:

There is a significant relationship between gustatory perception and certain parameters of quality of life in patients with advanced cancer.

Table 4.1 Impact of altered taste perception on QOL

Have the taste changes affected your eating habits? NS					
Response Category	Eat more food	Eat less food	Eat different foods	Eat at different times	No Change
n	1	16	14	2	2
%	3	46	40	6	5
Do you sometimes feel hungry but the taste puts you off? NS					
Response Category	All of the time	Frequently	Occasionally	No	Never feel hungry
n	2	7	7	14	5
%	6	20	20	40	14
Have the taste changes affected your general enjoyment of life? NS					
Response Category	Had a significant negative effect	Quite a lot	A little	No change	Improved
n	7	8	8	10	0
%	20	26	26	28	0
Have the taste changes affected those close to you? NS					
Response Category	Yes it has become a major worry	Yes it has caused friction	Occasionally it has been noticed	No	No close relationships
n	11	2	6	10	6
%	31	6	17	29	17

NS = Not Significant

Table 4.2 Patient responses stratified by altered taste perception

Do you ever feel too tired to eat?

NS

Response Category	All of the time	Often	Occasionally	Never	Less tired than before
% taste changes n=35	5	20	24	51	0
% no taste changes n=15	13	7	24	56	0

Has your illness affected the interest you take in your appearance?

NS

Response Category	Yes, I don't want to see myself	Yes, I rarely take an interest	No, should try harder	No, just the same	Take more care than before
% taste changes n=35	6	34	6	46	8
% no taste changes n=15	7	33	0	60	0

How often do you socialise with family and friends?

NS

Response Category	Frequently	Rarely, I am not up to it	I am not a very sociable person	I have lost interest in being sociable	Never, sadly I find it too exhausting
% taste changes n=35	80	17	3	0	0
% no taste changes n=15	67	27	6	0	0

Do you enjoy watching television, or reading a newspaper?

Chi-squared = 7.99, $p < 0.001$

Response Category	Frequently	Some days I do and some days I don't	Rarely, I cannot concentrate	Rarely, I never did	No
% taste changes n=35	43	17	30	3	7
% no taste changes n=15	47	41	6	6	0

Do you have a hobby, do you still enjoy it?Chi-squared = 15.4, $p < 0.01$

Response Category	Yes, no change	Some days I do	Rarely, I cannot concentrate	No, I have no energy	No hobby
% taste changes n=35	20	34	0	23	23
% no taste changes n=15	39	6	9	6	40

Do you ever feel tense and nervous?Chi-squared = 22.5, $p < 0.001$

Response Category	Most of the time	Quite often	Only when I go to the Doctor	Very rarely	Never
% taste changes n=35	20	34	0	23	23
% no taste changes n=15	29	6	6	6	53

4.3 Discussion

4.3.1 Taste changes and QOL

Results highlighted in this section identify aberrations of taste perception as a symptom that may impinge on QOL. This information has not previously been reported in patients receiving no active treatment and is pivotal in the management of symptoms associated with malignant disease in order to maximise patients' QOL.

The subjective information regarding aspects of QOL illustrated that for many patients altered taste perception was felt to have impinged on QOL. For some patients, irrespective of the magnitude of taste changes, this symptom was associated with appetite loss and changes in food selection which are key components of QOL.

A variety of responses to the question 'Have your taste changes affected your general enjoyment of life' were received. The majority of patients reported that diet played an important part in their life. This concern was extended into their period of illness when changes in taste perception and appetite were prevalent. In contrast, for the remaining patients, taste changes were not a priority whereas other predominant symptoms such as pain and nausea had a greater impact on QOL. These symptoms may also indirectly affect nutrient intake, nutritional status and subsequent QOL. The impact of altered taste perception was further explored in relation to specific daily activities. Although the majority of patients frequently enjoyed socialising, they reported that this symptom impinged on many social aspects of their life. In particular, patients reported a negative

impact on the enjoyment of food and the inability to participate in the social aspect of eating.

Altered taste perception may not directly influence QOL but indirectly as a consequence of contributing to other symptoms such as weight loss and fatigue. Weight loss is considered as a major factor influencing QOL in cancer patients receiving chemotherapy (Cohen and Mount, 1985). In this current study, weight loss and altered body image was associated with a lack of interest in appearance. It may not be totally surprising considering that body image was of prime concern for many patients as almost 75% of patients reported to have recently lost a considerable amount of weight. Time was allowed during the structured interview to discuss how this component affected patients' QOL. This was necessary to allow additional time to explore areas of concern that had arisen during questioning. The information in this current study suggests that altered taste perception may contribute to a negative effect on body image by reducing appetite that may contribute to weight loss.

In this study, almost half of the subjects (49%) experiencing taste changes reported that, fatigue affected their dietary intake. These data are explored further in chapter 6. Likewise, from this subjective information, tiredness and the lack of concentration appeared to interfere with the amount of time spent socialising and the interest in hobbies such as watching television or reading newspapers. This information also highlights the multifactorial nature of QOL.

The final question '*do you ever feel tense and nervous?*' allowed a more precise exploration of aspects of everyday life perhaps not previously captured by the other

questions that contributed to a period of tension. The cause of the feeling of 'tension' was gauged as an important indicator of QOL, allowing subjects to incorporate individual distinct values into the assessment process. Several issues, not included in the physical domain, such as social support, anxiety and depression were reported to have increasing importance since diagnosis. These issues are often the focus of QOL techniques.

4.3.2 QOL assessment tool

Where treatment is palliative, the contribution that is made by perceived gustatory and olfactory aberrations may have a great significance in terms of QOL and have a significant detrimental effect not only on the patient but also on the carer.

The interview style questionnaire was a non-invasive technique and easy to perform. This style of assessing QOL fulfilled one of the main aims of conducting research within patients with terminal disease that is, not impinging on the QOL of patients whilst assessing this variable (Maguire and Selby, 1989). The length of time taken to complete each question varied as it allowed the subjects to explore areas of concern with the two observers present. Although the questionnaire was based on validated questions from the HAD scale, numerical scoring was not validated within this population. Assumptions cannot be made as to the numerical weighting of quotations as individual question responses may have a different impact on QOL. In the present study, emphasis was focused on the physical domain, which addressed the impact of taste changes in relation to other physical symptoms such as tiredness, appetite, hobbies, and an interest in physical appearance. An inclusion of questions covering other domains of QOL for example work

practices would result in a lengthy measurement in this setting. The focus of the impact of altered taste perception would be lost amongst the numerous questions.

5.1 Introduction

Null Hypothesis (4): There is no relationship between gustatory perception and nutritional status in patients with advanced cancer.

This chapter provides up to date information on the nutritional status of 2 groups of elderly patients, one with advanced cancer receiving palliative care and a non-acutely ill group. Secondly, the relationship between nutritional status and gustatory perception is also examined. Body composition was determined using upper arm anthropometry, BIA and handgrip dynamometry in both the cancer and control groups.

5.2 Results

5.2.1 Comparison of nutritional status of cancer patients and control subjects

Upper arm anthropometric measurements of TSF, AMC and handgrip dynamometry were determined in both control subjects and cancer patients (Table 5.1 and Table 5.2). Body weight, when expressed as a percentage of mean reference data, was significantly lower in cancer patients (n=38) when compared to controls (n=36, $p<0.05$). Mean weight of controls was $60.8 \pm 2.4\text{sem}$ kg representing $95 \pm 3.51\text{sem}$ percentage of mean reference data (Lehmann *et al*, 1991). Control subjects did not report any significant amounts of weight loss (>10% usual weight in 3 months; table 5.1). All control subjects were above 50% of reference data for weight and handgrip (Lehmann *et al*, 1991; Burr and Phillips, 1993). Mean TSF represented 126% reference data. Indicators of muscle mass (AMC and

AMA), and also hand-grip dynamometry, indicative of muscle function, were significantly lower in cancer patients when compared with control subjects ($p < 0.01$, $p < 0.05$, $p < 0.05$ respectively).

Table 5.1 **Comparison of weight status of cancer patients and control subjects**

	Cancer Patients			Control Patients			p value
	n	mean	± sem	n	mean	± sem	
Weight (kg)	38	57.5	2.2	36	60.8	2.4	NS
Weight *	38	85.7	3.0	36	95.0	3.5	<0.05
Female weight (kg)	29	87.9	3.7	22	97.2	4.2	NS
Mindex	29	77.9	6.1	22	81.9	3.8	NS
Male weight (kg)	9	78.6	1.1	14	91.5	2.4	NS
Demiquet	9	75.1	1.0	14	77.5	8.7	NS

* Expressed as percentage mean reference data (Lehmann *et al* 1991, Burr and Phillips, 1993)

NS = Not Significant

Table 5.2 Comparison of anthropometric data of cancer patients and control subjects

	Cancer Patients			Control Patients			p value
	n	mean	± sem	n	mean	± sem	
TSF (mm)	44	12.1	1.0	40	14.1	1.1	<0.05
TSF Female (mm)	31	12.9	0.9	24	15.2	1.5	<0.05
TSF Male (mm)	13	10.2	1.3	16	12.5	0.7	NS
TSF *	44	87.1	8.6	40	126.7	8.6	<0.05
AMC (cm)	44	20.1	0.8	40	23.2	0.7	<0.05
AMC Female (cm)	31	22.2	0.6	24	25.3	0.8	<0.05
AMC Male (cm)	13	15.1	1.1	16	37.8	0.5	<0.05
AMC *	44	93.0	4.9	40	106.8	5.3	NS
AMA (cm ²)	44	352.4	24.9	40	440.7	27.6	<0.05
AMA Female (cm ²)	31	381.1	23.6	24	481.9	26.3	<0.05
AMA Male (cm ²)	13	181.0	26.7	16	491.6	27.9	<0.05
AMA *	44	93.8	6.6	40	131.6	7.8	<0.05
Hand grip (kg)	44	14.4	1.4	38	21.3	2.2	<0.05
Hand grip Female (kg)	31	17.6	1.2	22	19.6	2.4	<0.05
Hand grip Male (kg)	13	8.6	1.5	16	23.6	1.8	<0.05
Hand grip *	44	14.4	1.4	38	21.3	2.2	<0.05

* Expressed as percentage mean reference data (Lehmann *et al* 1991, Burr and Phillips, 1993)

NS = Not Significant

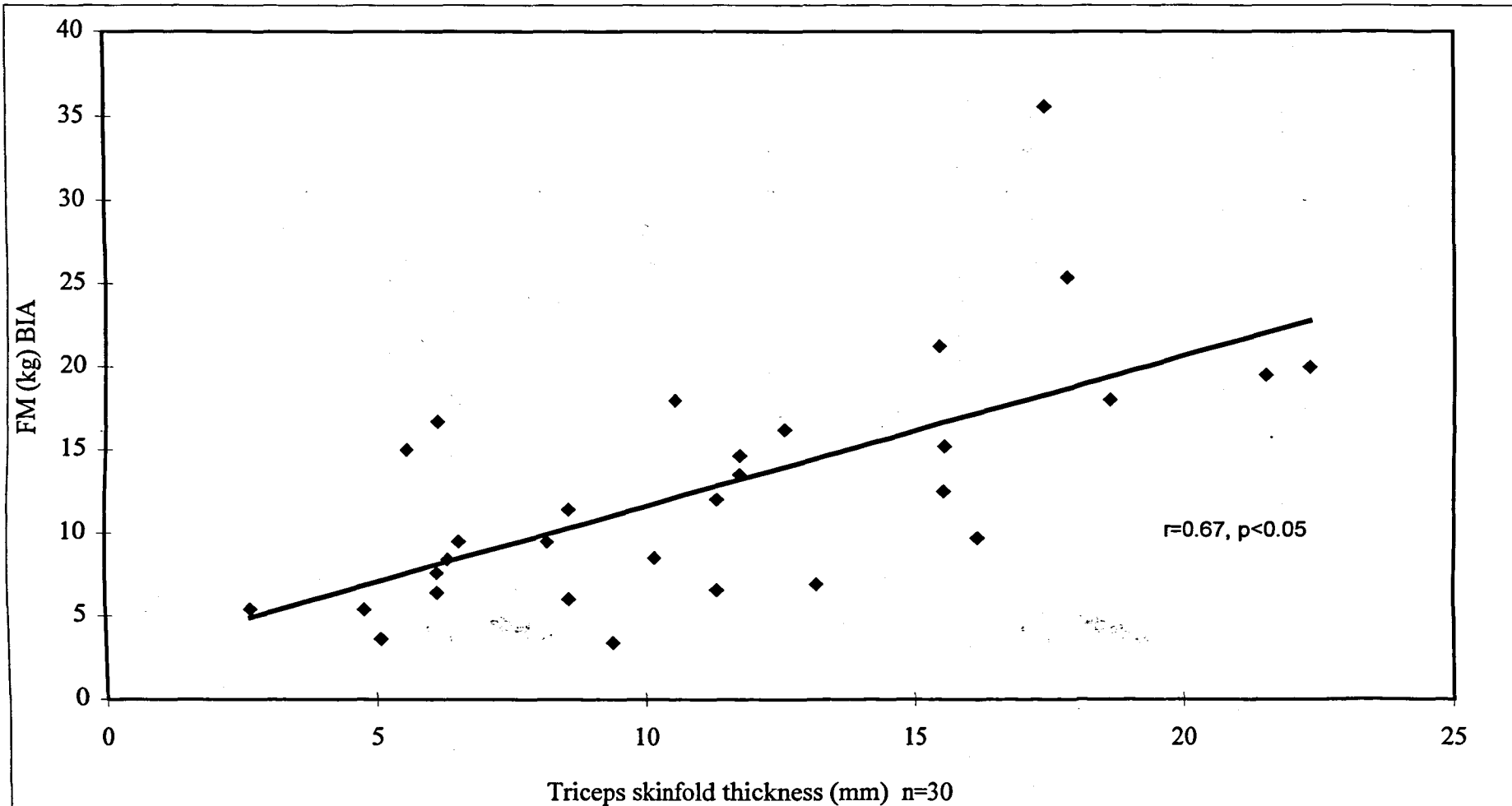


Figure 5.1 Correlation between estimates of FM by BIA and TSF techniques

BIA was performed in 38 cancer patients and 36 control subjects to further explore the nutritional status of both groups (Table 5.3). Significant peripheral oedema (n=5) and the inability to assess weight due to reduced mobility (n=18) excluded the remaining cancer patients from this nutritional assessment. Eight control subjects admitted for reduced mobility, were also excluded from this assessment.

Analysis of BIA parameters for both cancer and control groups are shown in table 5.3. When expressed in relation to body weight, no differences were noted between the two groups. Mean FM was significantly lower in patients with cancer as compared to controls ($20.0 \pm 1.7\text{sem kg}$ vs. $23.2 \pm 2.5\text{sem kg}$; $p<0.05$). No significant differences in both TBW and BCM were noted between both cancer patients and control subjects.

BIA and Anthropometric Parameters

The relationship between BIA and anthropometry within the group of advanced cancer patients was examined. TSF was positively correlated with measurements of FM derived from BIA ($r=0.67$, $p<0.05$, Figure 5.1).

Table 5.3 Comparison of BIA parameters of cancer patients and control subjects

BIA Parameters	Cancer patients n=38			Control Subjects n=36			p value
	mean	± sem	range	mean	± sem	range	
Fat Mass(kg)	20.0	1.7	3.4-35.6	23.2	2.5	5.5-38.3	ns
Fat Mass *	34.8	1.5	7.2-38.7	38.2	4.8	14.0-41.2	<0.05
Lean Body Mass (kg)	37.5	1.4	28.3-67.6	37.6	3.2	30.5-62.3	ns
Lean Body Mass *	65.2	1.3	62.6-93.2	61.8	1.8	58.8-86.0	ns
Total Body Water (l)	30.3	1.1	20.7-49.3	33.5	1.3	19.6-45.5	ns
Total Body Water *	53.6	1.8	45.7-68.9	55.0	1.2	21.0-52.0	ns
Body Cell Mass (kg)	17.9	0.9	3.6-27.5	19.7	1.3	6.5-49.4	ns
Body Cell Mass *	30.5	1.2	11.5-39.5	32.6	3.1	14.9-57.5	ns

* Expressed as a percentage of body weight

NS = Not Significant

Patients with cancer had a significantly lower mean muscle function as assessed by hand grip dynanometry ($14.4 \pm 1.4\text{sem kg}$) when compared to control subjects ($21.3 \pm 2.2\text{sem kg}$; $p<0.05$; Table 5.2). Positive correlation between muscle mass and function was observed between hand grip dynanometry and AMC ($r=0.46$, $p<0.05$; Figure 5.2) and hand grip dynanometry and weight ($r=0.61$, $p<0.001$; Figure 5.3).

Weight history of patients with advanced cancer

Weight was measured in 38 out of 56 cancer patients (73%). It was not practical to assess the weight of the remaining 18 patients with advanced cancer due to reduced mobility. Almost three quarters cancer patients ($n=27$) reported some degree of weight loss within the previous three months. Overall, the mean weight loss expressed as a percentage of usual body weight was $3.1 \pm 1.0\text{ sem \%}$ (range 0 – 23%) where eight patients lost more than 10% usual weight within the previous three months (mean loss $16.1 \pm 1.7\text{sem kg}$, range 11 – 23%). No significant difference in weight was noted between the male and females of both the cancer and control groups.

Weight loss was reported in the majority of patients with primary colonic carcinoma (8 out of 9 patients) and rectal carcinoma (5 out of 6 patients). Approximately, 50% ($n=6$) breast cancer patients had lost weight (mean loss $5.2 \pm 0.5\text{sem \%}$ weight within the previous three months). Measurements of weight and upper arm anthropometry in weight stable ($n=11$)

and weight losing cancer patients (n=27) are compared in table 5.4. In addition, weight losing cancer patients had significantly lower AMC and derived AMA measurements.

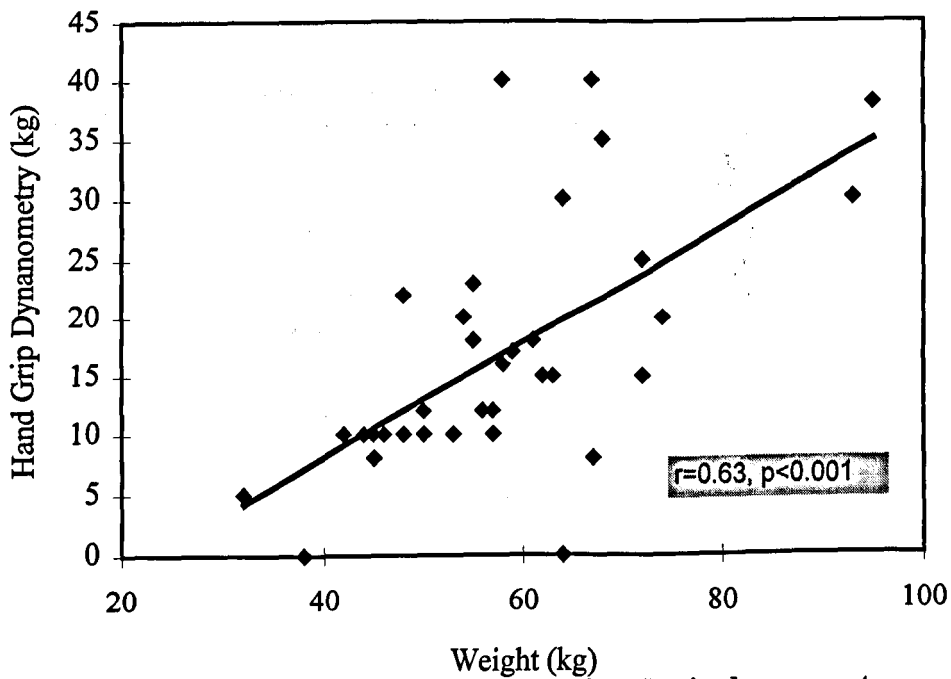


Figure 5.3 Correlation between hand grip dynamometry and weight of cancer patients

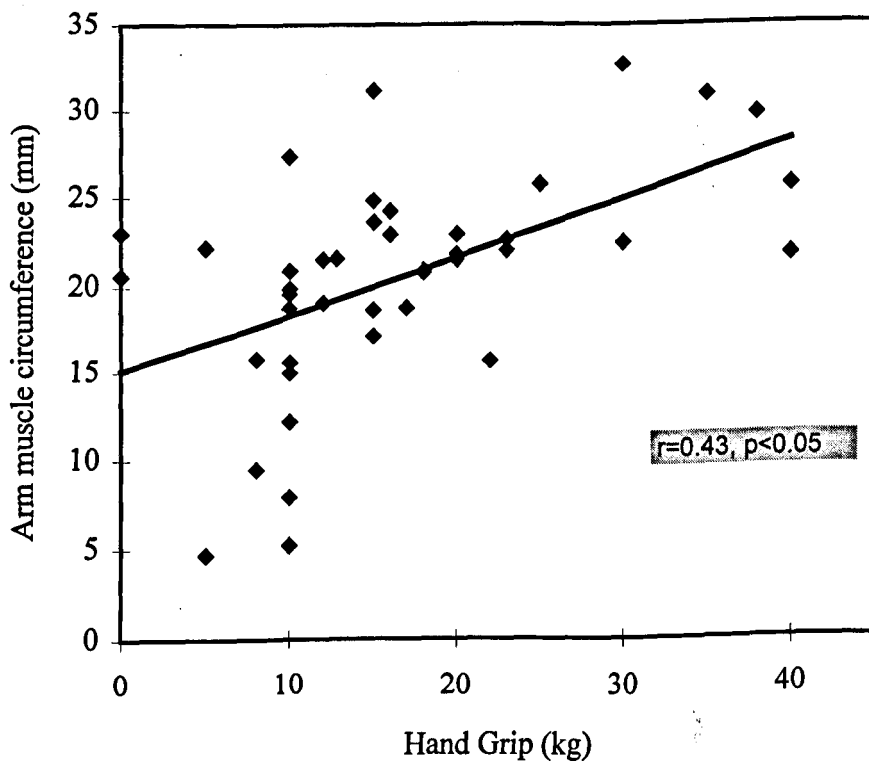


Figure 5.2 Correlation between hand grip dynamometry and AMC in cancer patients

Table 5.4 Anthropometric parameters of weight losing and weight stable patients with cancer

Anthropometric Parameter	Mean \pm sem		p value
	Weight Losing cancer patients(n=27)	Weight Stable cancer patients (n=11)	
Weight (kg)	56.5 \pm 2.4	60.4 \pm 5.6	NS
Weight *	85.7 \pm 3.5	85.6 \pm 6.7	NS
AMA(cm ²)	326.6 \pm 25.9	480.4 \pm 181.6	<0.05
AMC (cm)	19.3 \pm 1.1	23.5 \pm 1.5	<0.05
TSF (mm)	11.4 \pm 6.1	13.9 \pm 2.1	NS

NS = Not significant

* Expressed as a % mean reference data (Lehmann *et al* 1991; Burr and Philips, 1993)

5.2.2 Altered Taste Perception and its Relationship with Nutritional Status

The nutritional status of patients was stratified according to whether patients experienced altered taste perception. No differences in upper arm anthropometric parameters (TSF, AMC, and AMA) were noted between subjects stratified by taste changes (Table 5.5). Likewise, there were no significant differences in BIA parameters between these two groups (Table 5.6).

The weight history of cancer patients was explored in relation to the taste profiles. No associations between weight and any of the taste modalities (sweet, sour, salt and bitter) were noted. Patients reporting weight loss ($n=28$) exhibited a heightened ability to detect bitter taste compared to weight stable counterparts ($n=10$) and also compared to the control subjects ($p<0.05$; Mann-Whitney test, Figure 5.4). In addition, subjects who reported weight loss exhibited heightened bitter recognition thresholds compared to controls. This data suggests that cancer patients who presented with weight loss had an enhanced ability to detect bitter perception.

Based on this information, the null hypothesis (4) is rejected and the following hypothesis is accepted:

Patients reporting weight loss exhibited a heightened ability to detect bitter taste compared to weight stable counterparts and also compared to the control subjects.

**Table 5.5 Comparison of anthropometric parameters in cancer patients stratified
by subjective reporting of taste changes**

Subjective Reporting of taste changes						
	Reported taste changes			No taste changes reported		
	n	mean	± sem	n	mean	± sem
Weight (kg) n=38	27	59.4	3.2	11	53.9	2.4
% IBW*	27	86.3	4.9	11	84.6	3.4
TSF (mm) n=44	30	12.2	1.1	14	10.6	1.6
TSF *	30	83.9	10.0	14	81.6	13.0
AMA (cm ²) n=44	30	372.8	33.6	14	219.4	31.9
AMA *	30	93.7	9.0	14	87.4	9.0
Hand grip (kg) n=44	30	16.1	2.1	14	16.9	2.1
AMC (cm) n=44	30	20.8	1.0	14	18.6	1.6
AMC *	30	99.8	4.6	14	79.5	10.2

* Expressed as a % reference data (Lehmann *et al*, 1991; Burr and Phillips, 1993)

Table 5.6 Comparison of BIA parameters in patients stratified by subjective taste changes

Subjective Reporting of taste changes n=38				
	Patients reporting taste changes n=27		Patient not reporting taste changes n=11	
	mean	± sem	mean	± sem
Fat Mass (kg)	19.3	1.8	21.7	1.6
Fat Mass *	21.6	2.0	40.2	2.3
Lean Body Mass (kg)	43.7	2.1	36.3	2.1
Lean Body Mass *	61.3	1.7	74.7	2.1
Body Cell Mass (kg)	17.5	1.3	18.6	1.1
Body Cell Mass *	28.9	1.7	33.3	1.1
Total Body Water (l)	28.4	1.6	33.3	1.6
Total Body Water *	50.5	2.7	56.4	1.7

*** Expressed as a percentage of body weight**

5.3 Discussion

Examination of the nutritional status of patients with advanced cancer was made and compared with age matched controls. The group of elderly subjects were appropriate controls as none had evidence of metabolically active disease. In addition, no subjects reported any recent weight loss with mean anthropometric parameters above 50% of reference data.

5.3.1 Nutritional status of patients with advanced cancer

Body weight was lower in the cancer patients when compared to the controls and was significantly different when expressed as a percentage of reference data. The differences in weight status between cancer and control groups may be attributable to gender differences. However, weight expressed as mindex (Female) and demiquet (Male) body mass indices, revealed no differences between both groups.

The mean weight of the cancer group may not be representative of all of the group studied with advanced cancer as not all patients were weighed due to reduced mobility. Since the weight status between cancer and control groups was not significantly different this may suggest that in the presence of cancer, there is an expansion of the extracellular water which would result in an increase in weight. This is not supported by the body composition results that, using BIA, demonstrated no significant differences in the TBW component of the cancer patients as compared to the control subjects. Looking more closely at weight loss in the cancer group studied, BIA revealed a reduction in both FM

and LBM that highlights the components of weight loss and the value of assessing nutritional status using several assessment tools. Although there are limitations in the use of BIA as highlighted in chapter 1, these results support the anthropometric results and highlights a depletion of lean and fat mass in cancer patients compared to control subjects. Catalona and colleagues (1993), found that despite no significant changes in LBM:FM ratio, alterations in TBW occurred in cancer patients. Considering the evidence to suggest an expansion of extracellular water, the use of isotopes such as ^{77}Br (bromine) to determine BCM and $^3\text{H}_2\text{O}$ (tritium) for TBW would further explore the nutritional status of cancer patients. However, the use of isotope research to assess nutritional status may not be appropriate for use in the palliative care setting.

When evaluating nutritional status, it is important to consider weight in relation to the amount of recent weight loss rather than reference values of weight which, based on healthy adults, may have limited value in this area of research. Recent weight loss is indicative of changes in the clinical and nutritional status of these patients and adds a more dynamic perspective as comparisons are made from individual patients baseline. However, the accurate determination of weight change due to the course of the illness was limited as no records of weight were kept and therefore in this study, weight loss was assessed from the patients recalled pre-illness weight. It is acknowledged that there may be errors in establishing a precise degree of weight loss due to reduced memory function.

Almost three quarters of patients with advanced cancer reported significant weight loss that included 8 patients who lost more than 10% body weight in the previous 3 months (mean loss $16.1 \pm 1.7\text{sem } \%$). This is certainly an amount that may have a negative impact on

prognosis. A similar degree of weight loss has previously been reported by Falconer and colleagues (1995) who noted that in 21 patients with pancreatic cancer, weight loss was $18 \pm 2\text{sem \% mean weight}$ ($59.3 \pm 2.8\text{sem kg}$) as compared to 16 healthy controls who were weight stable (mean weight $72.4 \pm 3.6\text{sem kg}$).

The location of the tumour has also previously been associated with the degree of weight loss. However, in this study, weight loss was evident in patients with a variety of primary diagnosis categories including breast, lung, stomach, large bowel, ovary and pancreas. Approximately half of patients with breast cancer, one of the predominant tumours studied, experienced a substantial degree of weight loss in three months prior to assessment. Previously, studies in cancer patients have not demonstrated weight loss amongst subjects with this tumour type (Knapp *et al*, 1991). This may reflect the effects of symptoms associated with advanced stage of disease that impinge on the dietary intake and alterations in metabolism. In this present study the weight loss may merely reflect the advanced stage of disease progression in patients with terminal malignancy. Recently, Wigmore and colleagues (1997) noted weight loss (10-20% pre-illness weight) in a group of patients with advanced unresectable pancreatic cancer. This greater degree of weight loss may be affected by pancreatic involvement that would further exacerbate weight loss experienced by patients.

Weight loss demonstrated in this study was reflected by lower indices of upper arm anthropometry and hand grip dynamometry when compared to controls. Within the cancer group, muscle mass as indicated by AMC and AMA were significantly lower in patients who had lost weight compared to those who were weight stable. In addition,

anthropometric data indicated that self-reported weight loss was reflective of a lower lean body mass indicated by both arm muscle circumference and arm muscle area.

Moreover muscle function as demonstrated by handgrip dynamometry was lower in cancer patients compared to control subjects. These results indicated a loss of muscle mass and associated muscle function in patients studied. These results are in contrast to a study of cancer patients by Watson and Salmon (1980) which indicated a relative sparing of lean tissue in weight loss of cancer patients reflecting a state similar to simple starvation. Although it is unclear as to the extent of the disease in that study, body fat mass which was assessed by skinfold thickness and isotope tracer technique was almost entirely depleted. Likewise, Deurenberg and colleagues (1989) indicated that a similar degree of weight loss (10kg), was reflective of 70-80% loss of fat mass.

The majority of studies in cancer patients have excluded those with advanced stage of disease and hence these results contribute significantly to the understanding of the nutritional status of cancer patients experiencing weight loss in the latter stage of the disease. Considering the present results, a loss of muscle mass denotes a catabolic state. Further investigation of the mediators of weight loss in cancer namely pro-inflammatory cytokines and the associated inflammatory response is fully discussed in chapter 7.

5.3.2 Gustatory perception and nutritional status

Following determination of the nutritional status of patients with advanced cancer, the taste perception profiles of these patients were examined to investigate any relationship with nutritional status.

Within the cancer group, no differences were noted in the nutritional status of patients stratified by subjective taste reporting. In a study by Walsh and colleagues in 1982, weight loss was not associated with alteration in taste perception. It is perhaps not possible to distinguish the exact impact of altered taste perception on the nutritional status as other symptoms characteristic of advanced cancer such as pain and nausea may have a confounding impact on an already poor nutritional status. However, it is acknowledged that any measurable impact of altered taste perception on food preference and dietary intake will have an impact on the nutritional status of patients.

Bitter taste perception and weight status

Conversely, the impact of nutritional status and in particular any change in nutritional status associated with a dynamic disease state on taste perception was also considered. Considering the high prevalence of weight loss in almost three quarters of the cancer patients, this parameter was examined in relation to taste perception. Interesting results are reported in relation to weight losing patients and bitter taste perception. Cancer patients who reported a significant degree of weight loss (>10% pre-illness weight) exhibited an increased ability to both detect and recognise bitter taste compared to control subjects. This observation has not previously been reported in a heterogeneous group of cancer patients receiving only palliative care and suggests that subjects with cancer who presented

with weight loss have a greater aberrant response to bitter taste. No differences were noted with respect to the other three primary tastes, salt, sour and sweet. This observation is in line with findings by Ovesen and colleagues in 1991 who noted that patients with significant weight loss had lower bitter thresholds when compared to weight stable cancer patients. These observations were made in patients with small cell lung cancer where 44% subjects exhibited a significant amount of weight loss (median weight loss 5kg). It is important to note the difference between both studies namely, the heterogeneous nature and advanced stage of disease in this current study.

Weight loss may be indicative of the metabolic response occurring in patients with advanced cancer and associated inflammatory response (Bernstein, 1994). Therefore, the results of this current study suggest that weight loss is associated with a heightened bitter taste perception. The mediators of the inflammatory response which cause weight loss may be associated with altered taste perception and will be further explored in chapter 7. Alternatively, these results may indicate that weight loss and an associated breakdown of LBM, which provides substrates for gluconeogenesis, may influence taste perception. These may alter circulating amino acid profiles to such extent that they influence hypothalamic feeding centres. An imbalance at this level may influence central taste perception.

5.3.3 Assessment of nutritional status of advanced cancer patients

It is perhaps appropriate to discuss the use of the tools chosen to measure nutritional status in this current study. Methods used to determine nutritional status in this study have previously been applied in the investigation of body composition of patients with advanced

cancer (Wigmore *et al*,1996). A few points may be made with regard to the use of the chosen tool from observation in this current study.

BIA proved to be a useful non-invasive bedside tool in this subject setting as it was quick to perform. Although results mirrored anthropometric analysis, the accuracy of BIA in determining body composition is limited in patients where there are changes in fluid compartments that may provide erroneous results and create a bias in the estimation of total body water. Although in this current study, five patients were excluded due to significant peripheral oedema, the degree of changes in fluid balance in the remaining subjects were not accurately known.

Within the cancer group, TSF was the only non-invasive procedure performed in the presence of oedema as other sites such as the sub-scapular and iliac crest are less accessible and more prone to oedema and would therefore influence results. In addition, incorporation of measurements at other sites increasing the length of assessment would perhaps reduce recruitment or lead to incomplete data collection for patients. Despite errors in the measurement of fat mass by TSF, the assessment was standardised in order to reduce the inter-subject errors.

Likewise, hand grip dynamometry appeared to be a useful bedside tool in assessing muscle function. In patients with advanced cancer, weakness, asthenia and fatigue are common symptoms and therefore the hand grip dynamometer has an important place in assessing the functional status of these patients. This may also be useful in the assessment of QOL, of which functional status is an integral component.

Chapter 6 examines the association between the second component of nutritional assessment, namely, dietary intake and taste perception.

6.1 Introduction

Null Hypothesis (5): There is no relationship between gustatory perception and dietary intake in patients with advanced cancer.

This chapter provides detailed information regarding the energy and macro-nutrient intakes of a group of randomly selected patients with advanced cancer receiving palliative care (n=23). These are compared with a group of healthy elderly patients within a geriatric assessment unit (n=16). In addition, the relationship between dietary intake and taste perception was also investigated. The amount of food consumed was determined using a three day weighed intake technique and then converted to macro-nutrient intake using Comp-eat dietary analysis package (Nutrition Systems, London). In addition, actual energy intakes were compared with estimated requirements.

6.2 Results

6.2.1 Dietary intake of cancer patients and control subjects

Macro-nutrient intake of cancer patients compared to control subjects

Differences in dietary intake were noted between the cancer and control groups. This was reflected in a significantly lower carbohydrate intake in cancer patients ($90 \pm 10\text{sem g}$) compared to controls ($176 \pm 12\text{sem g}$; $p < 0.05$). Likewise, the mean intake of fat ($41 \pm 10\text{sem g}$; $p < 0.05$) and protein ($35 \pm 8\text{sem g}$; $p < 0.05$) of the cancer patients were

significantly lower as compared to controls (60 ± 5 sem g and 67 ± 5 sem g respectively, $p < 0.05$). However, when these differences were expressed as a percentage of total energy intake, cancer patients had a significantly lower percentage intake of carbohydrate and greater percentage of fat compared to control subjects ($p < 0.05$). Protein intake, expressed as a percentage of energy intake, was lower in cancer patients compared to controls.

Macro-nutrient intake was compared with Dietary Reference Values (DRV; Department of Health, 1991). Within the cancer group, 21 out of 25 subjects consumed less than 80% DRV for energy. In addition, 17 out of 25 patients did not meet the DRV for protein. All control subjects had a dietary intake greater than 70% reference data for energy (mean intake 75.2% EAR), fat (mean 79.1% RNI) and protein intake (74.3% RNI).

When assessed in relation to weight, mean energy intake was significantly lower in the cancer group (0.06 ± 0.05 sem MJ/kg body weight) as compared to the controls (0.10 ± 0.01 sem MJ/kg body weight). Within the cancer group, a correlation was noted between energy intake and weight status ($p < 0.05$, Figure 6.1).

Dietary intakes of cancer patients were stratified by primary tumour diagnosis. Energy intake as expressed in relation to body weight was significantly lower in patients with breast carcinoma ($p < 0.05$) and large bowel carcinoma (colon and rectum, $p < 0.05$) compared to control subjects.

Predicted dietary energy requirements

Predicted energy requirements were estimated using Schofield equation (BMR). A physical activity value applied appropriate for both cancer and control groups, was applied to BMR (Table 6.2). A physical activity level of 1.3, appropriate for sedentary adults was used in the calculation. For the cancer patients, 65% consumed less than the required energy intake compared to 78% of the control group.

Dietary intake and fatigue associated with advanced cancer

Dietary intake was assessed in relation to fatigue in patients with advanced cancer. Scores were derived from responses to the question 'Do you ever feel too tired to eat?'. Although not statistically significant, patients who reported some degree of fatigue had lower energy intakes (mean $3.3 \pm 0.4\text{sem MJ/day}$) compared to those who did not report any fatigue (mean $4.0 + 0.72\text{sem MJ/day}$). Likewise, mean protein intake was lower in patients who reported tiredness ($33.7 + 5.2\text{sem g/day}$) compared to patients who did not report this symptom ($43.4 + 4.5\text{sem g/day}$) (Chi-squared=10.02, $p<0.05$). This data suggests that increased tiredness may be associated with reduced dietary intake in this cohort.

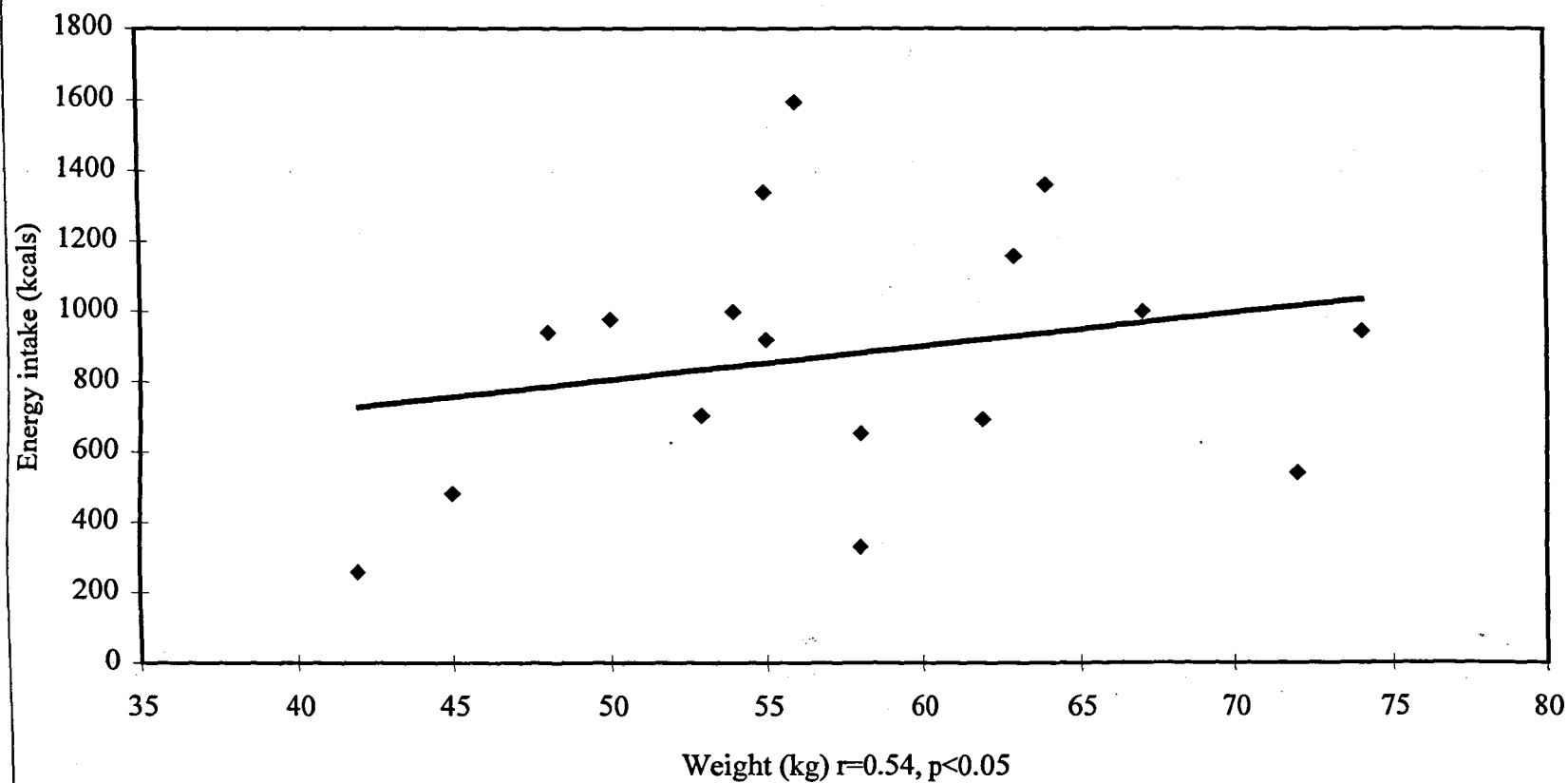


Figure 6.1 Correlation between energy intake and weight status in patients with advanced cancer

Table 6.1 Dietary intake of cancer patients and control subjects

Dietary Intake	Cancer Group			Control Group			p value
	n=23			n=16			
	mean	± sem	range	mean	± sem	range	
Energy MJ	3.5	0.3	1.0 - 6.7	6.1	0.4	2.6 - 8.9	p<0.005
Carbohydrate	90	10	28-168	176	12	75-261	p<0.05
% energy intake	40.9	1.0	24.5-50.9	43.9	0.1	38-51	p<0.05
Fat	41	10	13-84	60	5	28-103	p<0.05
% energy intake	43.7	1.1	36.2-57.7	38.3	1.4	24-48	p<0.05
Protein	35	8	10-73	67	5	22-92	p<0.001
% energy intake	16	3	12-21	18	1	13-26	NS

NS = Not significant

Table 6.2 **Actual and estimated energy intake stratified by sex**

	Cancer patients (10 Male, 13 Female)			Control patients (5 Male, 11 Female)			p value
Males	mean	± sem	range	mean	± sem	range	
Energy MJ	3.8	0.2	2.3-6.7	6.3	0.4	5.2-8.9	p<0.05
Estimated energy intakes *	5.3	1.3	4.5-6.6	7.3	0.5	6.5-9.2	p<0.05
Females	mean	± sem	range	mean	± sem	range	
Energy MJ	3.3	0.3	1.0-5.9	6.0	0.3	2.6-7.9	p<0.05
Estimated energy intakes *	5.1	1.2	4.4-6.7	6.6	0.5	5.2-7.3	p<0.05

* Estimated using Schofield equation (Schofield, 1985) x Physical activity level (1.3,
Department of Health, 1991)

6.2.2 Impact of altered taste perception on food choice

Three out of 35 patients who reported taste changes were not able to associate their taste aberration to any particular taste. Of the remainder, 19 patients described a general blunting of taste. Of 22 patients who reported specific alterations in taste perception, six described these changes as an increase in the sweet perception of certain food items and four patients reported avoiding sweet tasting foods. Ten patients reported an increased bitter taste perception of foods and subsequently avoided meat (n=4), chocolate (n=4) and tea (n=2) products. In addition, three patients who reported heightened salt perception associated this with a reduced consumption of certain salty food items.

6.2.3 Dietary intake and taste perception

The reporting of alterations in taste perception by patients was examined in relation to dietary intake of patients with advanced cancer. Patients who exhibited early bitter taste recognition had a significantly lower mean percentage energy contribution from protein in their diet (15% versus 18%, $p < 0.05$; Table 6.3). This was also noted when patients were stratified by subjective changes in bitter taste perception (Table 6.4). Although not statistically significant, the mean energy intake for patients who reported changes in bitter taste perception was 3.2 ± 0.7 sem MJ/day compared to 4.6 ± 0.4 sem MJ/day in patients who did not report these changes. Likewise, the mean macro-nutrient intake of protein, fat and carbohydrate were also lower in the group who reported an alteration in bitter taste perception as compared to the patients who did not report any taste changes.

Based on this information, the null hypothesis is rejected and the following hypothesis accepted:

Advanced cancer patients exhibiting early bitter taste recognition thresholds have a significantly lower mean percentage energy contribution from protein in their diet.

Table 6.3 Bitter recognition thresholds and dietary intake of cancer patients

Nutrient	Patient recognising bitter taste at threshold 1-4 n=10		Patients not recognising bitter taste at any level n=25	
	Mean	± sem	Mean	± sem
Energy MJ	4	1	3	1
Fat (g)	67	7	51	5
% energy Fat	40	1	44	4
Protein (g)	38	6	31	6
% energy Protein *	15	2	19	2
Carbohydrate (g)	99	17	78	15
% energy Carbohydrate	42	2	40	3

*** p<0.05 between cancer patients and control subjects**

Table 6.4 Nutrient intake of cancer patients stratified by subjective bitter taste changes

	Bitter taste changes not reported n=25		Bitter taste changes reported n=10	
	Mean	± sem	Mean	± sem
Energy	4.6	0.4	3.2	0.7
Fat (g)	49	9	40	6
% energy Fat	44	1	44	2
Protein (g)	43	7	30	4
% energy Protein *	18	1	15	1
Carbohydrate (g)	105	18	83	11
% energy Carbohydrate	39	1	40	2

* $p < 0.05$ between cancer patients and control subjects

6.3 Discussion

6.3.1 Comparison of dietary intake of cancer and control groups

This study conducted in the hospice setting, is one of few studies that has assessed the dietary intake of a group of patients with terminal disease using the weighed intake technique. This current study has assessed the impact of symptoms such as altered taste perception on dietary intake, which allows more appropriate dietary management in patients with advanced cancer. Few studies have accurately documented the dietary intake of patients with advanced cancer. This is mainly due to the difficulties in using a non-invasive technique to assess dietary intake and merely an acceptance of the fact that in terminally ill patients, nutritional intervention is futile and therefore unnecessary to assess dietary intake.

This current study assessed the impact of alterations in taste perception on the dietary intake and food selection of patients with advanced cancer. The dietary intake of the cancer patients was compared with that of the healthy control subjects, to subsequently examine the association between altered taste perception and dietary intake. The dietary intake of the group of cancer patients was considerably low with regard to macro-nutrients when compared to both the control group and the estimated energy requirements. Although, reference data was age and sex matched, it may be more appropriate to consider the dietary intake of the cancer patients in relation to reference data based on an institutionalised group. It is important to note that, differences exist in the provision of meals within both the hospital and hospice settings. In this present study, the control group

were provided meals from a pre-plated system whereas the hospice adopted a bulk system of food provision in which the type and quantity of food were chosen at each mealtime. However, this does not deter from drawing comparisons between the two groups as a choice of food items and portion sizes for each meal time was provided with each group, allowing individual selection of food items. The three day weighed intake technique has been shown to reflect macro-nutrient status accurately (Bingham, 1991). However, micro-nutrient status was not assessed as this would have required a longer period of dietary recording.

When cancer patients were stratified by tumour diagnosis, patients with breast and large bowel cancer demonstrated lower energy intakes as compared to controls. This correlated with the considerable degree of weight loss noted in more than half of breast cancer and almost all of patients with large bowel cancer. To a certain extent these results demonstrate the effects of reduced intake on weight loss highlighted in chapter 5, weight loss was evident in over half patients within this group of cancer patients. However, as previously mentioned, despite adequate energy intake for anabolism, cancer patients may often fail to gain weight.

Weight status was positively correlated with energy intake which is a unique finding using an accurate method to estimate dietary intake. Likewise, Grosvenor and colleagues (1989) noted that dietary intake, as expressed in relation to pre-illness body weight, was significantly lower in patients who were weight losing as compared to their weight stable counterparts. Ames and colleagues (1992) using a one day recall combined with a three day food record intake method, observed lower dietary intakes in patients with cancer

compared to control subjects. Giacosa and colleagues (1996), measuring food intake over a period of three days noted a greater energy intake than that measured in this current study. In this investigation by Giacosa's team, it is unclear as to the extent of disease progression or the presence of symptoms that may impinge on dietary intake. In this current study, the lower dietary intakes are reflective of an advanced stage of disease and using the weighed intake method to determine dietary intake.

There are many acknowledged limitations when making comparisons of dietary intake between studies due to the heterogeneous nature of subjects and the assessment tools used. Few studies have investigated the dietary intake of patients receiving palliative care, using a three day weighed intake method because it is time consuming and requires a degree of expertise. The dietary intake of the group of cancer patients measured in this current study is more likely to be representative of weight losing cancer patients experiencing altered taste perception because of the more stringent methodological approach used. These cancer patients have lower energy intakes than the elderly counterparts and contributes to loss of body mass.

Factors influencing the dietary intake of patients with advanced cancer

Examination of the impact of altered taste perception on dietary intake, revealed that other symptoms of advanced disease that may contribute to a reduced dietary intake need to be considered. It may be equally difficult to isolate the effects of tiredness on the dietary intake of patients experiencing a variety of symptoms associated with the disease. However, in this current study, fatigue was associated with low dietary intakes in cancer

patients. A lower energy intake was noted in patients who reported frequent episodes of fatigue as compared to those who did not report any changes in fatigue. This suggests a negative effect of symptoms such as fatigue on the dietary intake of patients with advanced cancer and illustrates another barrier to the successful achievement of recommended dietary intakes.

Other symptoms associated with advanced cancer may impinge on dietary intake. Feuz and Rapin (1994) highlighted that the dietary intake of patients increased following adequate pain control. However, patients recruited to this present study had good pain control at the time of assessment. Further studies are required to assess changes in intake over a longer period and to assess the impact of symptom control on dietary intake. In order to record dietary intake over the course of the illness, a visual analogue tool would provide a non-invasive type of assessment in this patient population to gauge intra-subject changes using baseline assessments.

6.3.2 Impact of altered taste perception on dietary intake

A main aim of this study was to examine the impact of altered taste perception on the dietary intake of patients with advanced cancer. Almost half of cancer patients attributed a reduction in food intake directly to changes in taste perception. This is very important considering that although dietary intake was objectively measured, there appeared to be no difference in the total macro-nutrient intake of patients experiencing or not experiencing taste changes. This may suggest that intake was reduced due to altered taste perception in

patients whose intake was not already compromised by the disease. However, this would be assessed by longitudinal measurement of macro-nutrient intake.

Protein intake and taste perception

An inverse relationship was noted between salt taste perception and protein intake where patients with high salt threshold that is, a low sensitivity to salt, had a lower intake of protein. It is not clear as to whether the low protein intake resulted in a reduced ability to perceive salt taste. In an animal study by Ohara (1994), suppressed salt perception was associated with a protein deficiency state perhaps indicating that changes in taste with respect to salt in a cancer population is not due to undernutrition *per se*.

Moreover, in this current study a significant number of patients who reported an increase in the bitter taste of certain food items such as meat and coffee had a lower protein intake when compared to patients who did not report any changes in bitter perception. A possible explanation is that patients with alterations in bitter perception consequently avoided foods with bitter compounds that are generally high protein foods such as meat. DeWys and Walters (1975) suggested that the correlation between meat aversion and lowered bitter threshold may be due to the amino acid, polypeptide or purine content of meat, compounds which in the pure form, have a bitter taste and hence in patients with heightened bitter thresholds may elicit an enhanced bitter sensation. Another explanation, suggested by Strohl (1993), is that the tumour may release circulating amino acids that have a bitter taste which stimulate a bitter perception. Subsequently, negative signals that are transmitted from the oral cavity when other bitter foods are eaten, may inhibit the appetite centre. If

this were the case then patients able to detect bitter taste would be expected to have a lower intake. However, this is not the case as patients are merely more selective in their food choice that may not significantly change their total energy or macro-nutrient intake. This study highlights that the alterations in taste perception have an impact on food selection that would impact on subsequent dietary intake.

6.3.3 Impact of taste changes on food selection

In this current study, changes in food selection, perhaps related to altered taste perception, were widely reported by patients with advanced cancer. A general loss of taste was associated with change in the intake of a variety of foods that subjects had enjoyed prior to the onset of any taste aberrations. Increased sensitivity for sweet perception was reflected in the avoidance of sweet foods. In contrast, one patient found sweet foods more appealing and pleasant due to reduced sweet sensitivity. This is an important consideration with regard to the role that the enjoyment of food contributes to QOL in terminally ill patients.

It may be difficult to evaluate the impact of alteration in gustatory function on nutrient intake without knowing the extent to which taste changes influence food selection. Trant and colleagues (1982) suggested that it might be tenuous to extrapolate from simple aqueous medium to complex food media. The link between taste thresholds and food selection have previously been disputed by Kamath and Booth (1983) where the authors highlighted that food selection was not solely dependant on taste perception. Other factors such as texture and aversions to food associated with periods of treatment play an important role in food choice of patients with advanced cancer. However, these patients

were not receiving active treatment and the impact of treatment associated food aversions were not investigated further in this population. However, in subsequent stages of this study, objective measures of taste perception provide a basis to measure the impact of any intervention.

Alterations in food selection may have a secondary impact on the quantity of food consumed but it is beyond the scope of this current study to investigate how specific food items that are avoided contributed to the overall energy and macro-nutrient intake. These results have highlighted the potential impact that taste perception has on the selection of food items and the subsequent enjoyment of food as reported by these patients.

Bitter taste perception and food selection

Focusing on bitter taste perception is important as patients who reported changes in taste perception had significantly heightened sensitivity to bitter. However, approximately two thirds of taste changes reported by patients were specific to bitter perception and foods subsequently avoided were associated with bitter tasting foods. Ten patients reported the avoidance of food items characterised by bitterness that included; meat, tea, coffee and chocolate. Moreover, as highlighted in chapter 3, patients with advanced cancer demonstrated significantly lower thresholds for bitter taste, denoting heightened bitter taste perception compared to controls. The results of this current study are similar to that first published over 25 years ago by DeWys (1974) who noted an avoidance of meat products in almost one third of a heterogeneous cancer group. Likewise, Walsh and colleagues (1982) using a structured questionnaire found that almost half of patients who reported altered

taste perception, also reported aversions to meat. Similar foods such as meat and coffee are common targets of learned aversions in cancer patients (DeWys, 1974). Many of these studies do not control for the impact of treatment on taste perception and hence food selection. This current study uniquely highlights the impact of altered bitter taste perception, not attributed to chemotherapy or radiotherapy, on the food selection of a group of advanced cancer patients.

7.1 Introduction

Null Hypothesis (6): There is no relationship between gustatory perception and blood cytokine concentration and gustatory perception.

This chapter provides information regarding the plasma cytokine levels and associated acute response in a group of 37 patients with advanced cancer. Within this group, the association between cytokine response and taste perception was investigated. Plasma cytokine levels (TNF α , IL-1 β and IL-6) were measured by ELISA technique. Albumin was measured by an automated bromocresol green dye binding technique. In addition, serum CRP used to denote the presence of an acute phase response was measured by a competitive binding immunoassay.

7.2 Results

7.2.1 Biochemical Analysis

Serum CRP

Used in conjunction with serum albumin concentration, serum CRP denoted the presence of an inflammatory response. The mean albumin concentration of patients with cancer was within a normal range (28.7 ± 1.3 sem g/l). An inflammatory response was indicated by an elevated CRP (>10 mg/l) in patients with albumin concentration within the normal range (Table 7.1). Nine patients with advanced cancer exhibited such a response. CRP analysis

performed on control patients indicated that all patients had a CRP < 10mg/l (mean CRP 5.4 ± 1.2 sem).

Plasma Cytokine concentration

Cytokine analysis was performed on samples obtained from the patients with advanced cancer. Plasma TNF α concentrations ranged from levels that were not detectable in assay (n=6) to a level of 42.38pg/ml. Mean values and ranges for all cytokines (IL-1 β , IL-6, TNF α) are noted in table 7.1. Correlation analysis indicated a positive correlation of CRP with the cytokines, TNF α ($r=0.59$, $p<0.05$; Figure 7.1) and IL-6 ($r=0.69$, $p<0.05$ Figure 7.2). In addition, TNF α correlated with IL-6 ($r=0.74$, $p<0.05$; Figure 7.3). Patients with an inflammatory response (n=9, CRP>10g/l) exhibited higher TNF α levels (mean 27.6 pg/ml \pm 4.62 sem pg/ml) as compared to patients not mounting this response (mean 9.62pg/ml \pm 2.55sem pg/ml; $p<0.05$).

Table 7.1 Biochemical analysis of samples obtained from cancer patients

Biochemical parameters					
	Serum	Serum	Plasma	Plasma	Plasma
	CRP	Albumin	IL-1β	IL -6	TNFα
n	37	37	37	37	37
Method	Immunoassay	Bromocresol green dye binding	ELISA	ELISA	ELISA
Unit	mg/l	g/l	pg/ml	pg/ml	pg/ml
Mean	7.42	28.7	3.22	30.65	15.38
\pm sem	2.2	1.3	1.07	5.34	2.72
Range	<1.5 - 17.4	25.1 -33.4	0*-28.5	0.5-114.8	0*-42.38

* Not detectable in assay technique

7.2.2 Cytokines and dietary intake

No correlation between the concentrations of the cytokines $\text{TNF}\alpha$ and $\text{IL-1}\beta$ with macronutrient intake were noted. However, in 23 cancer patients, plasma IL-6 concentration showed a positive correlation with dietary fat intake ($r=0.61$, $p<0.05$; Figure 7.4) In contrast, a negative correlation with carbohydrate intake and IL-6 was noted ($r=-0.53$, $p<0.05$; Figure 7.5), indicating that increasing concentrations of IL-6 were noted in patients with highest dietary fat intake.

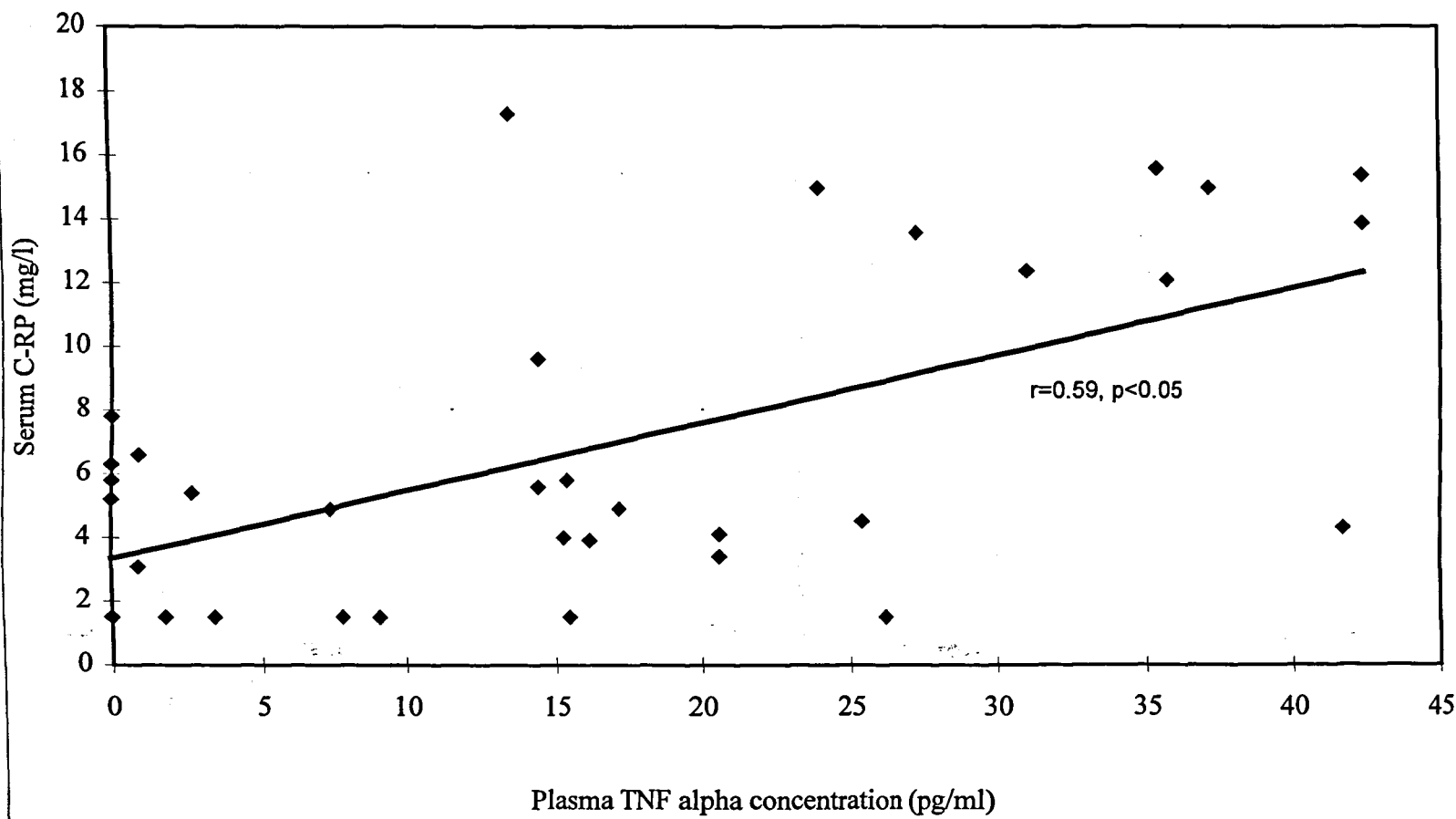


Figure 7.1 Association between plasma TNF alpha and serum CRP

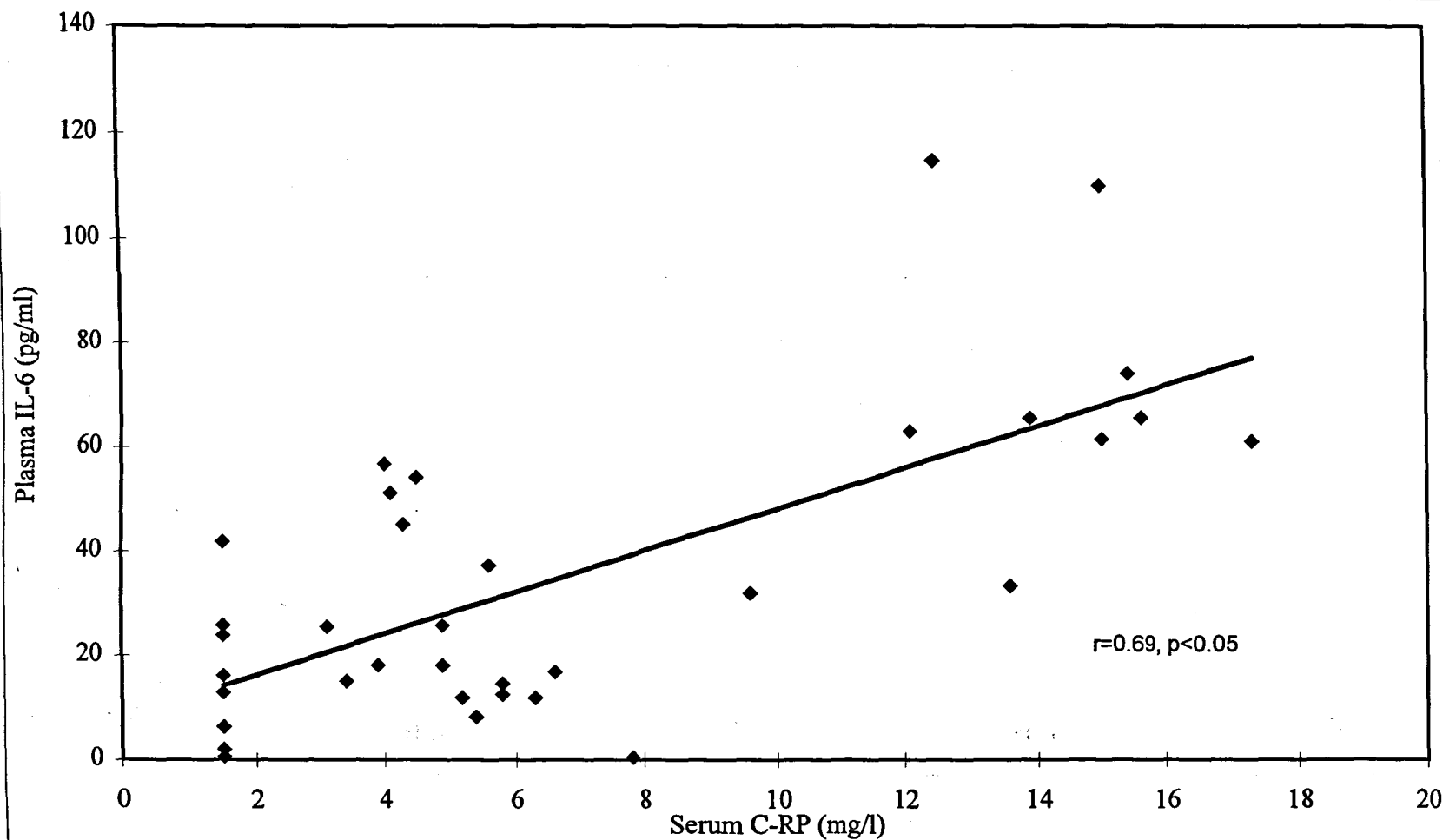


Figure 7.2 Correlation between serum CRP and plasma IL-6 concentrations

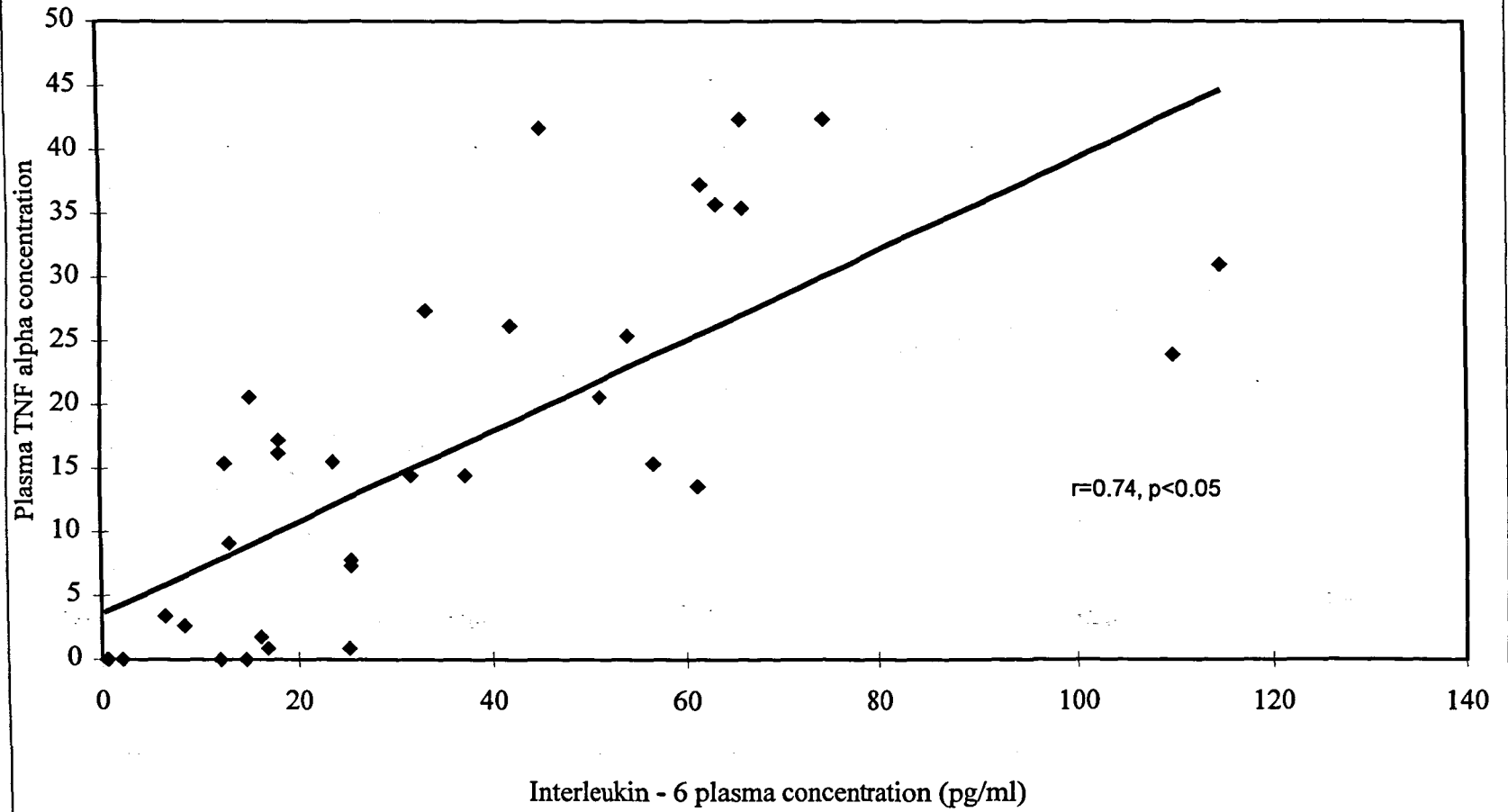
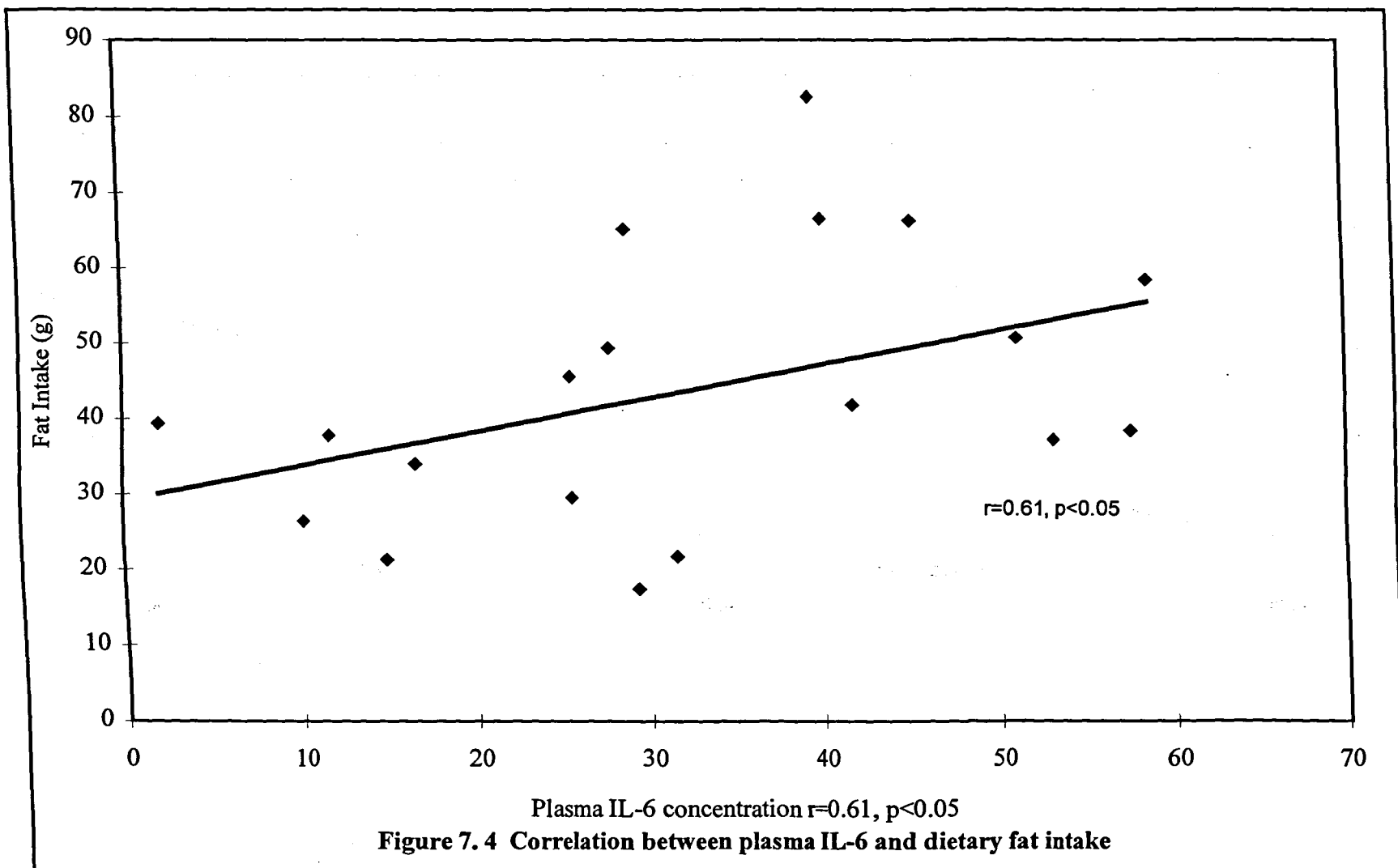


Figure 7.3 Correlation between plasme TNF alpha and IL-6 concentrations



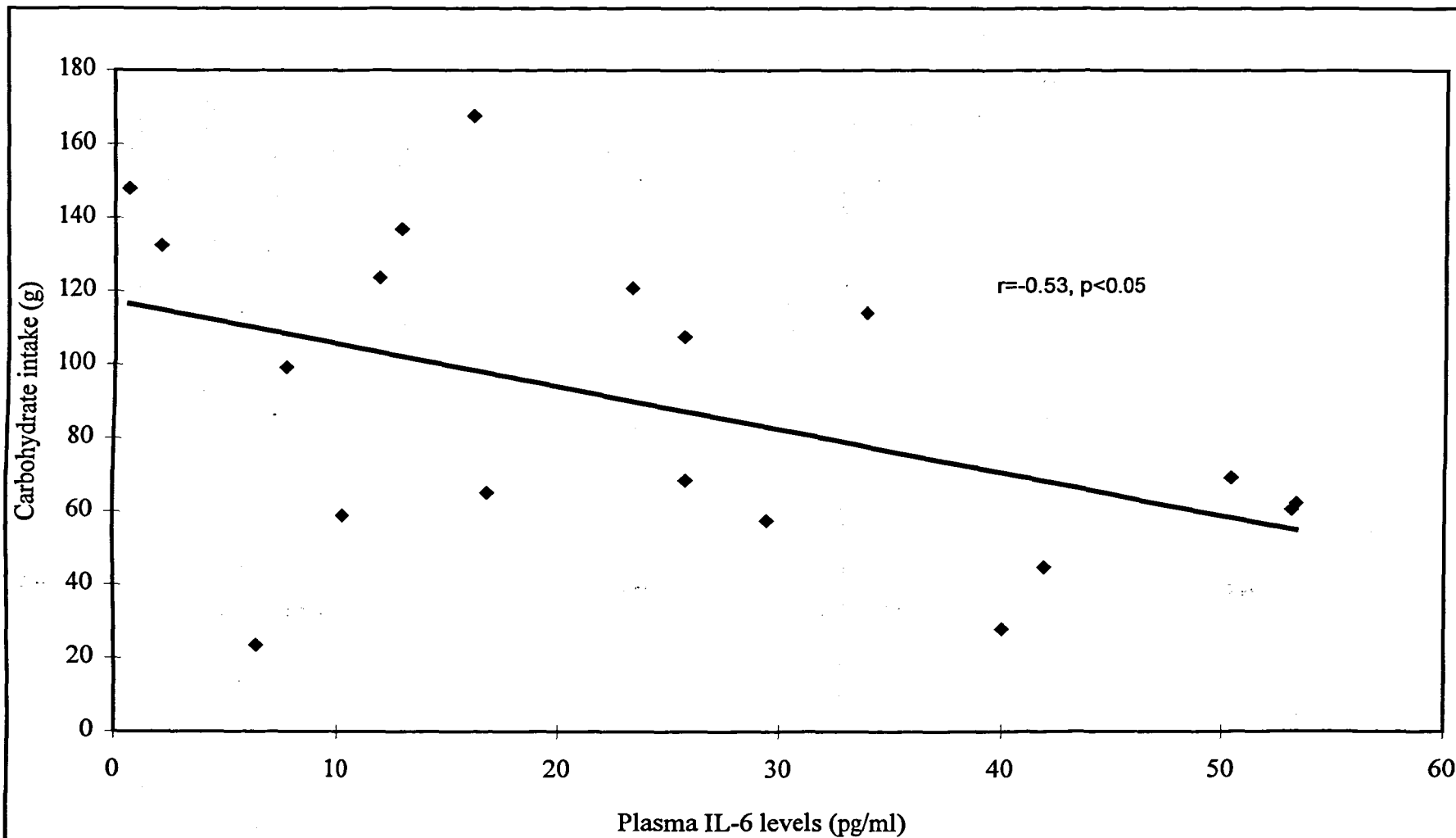


Figure 7.5 Correlation between plasma IL-6 concentration and carbohydrate intake

7.2.3 Cytokines and taste perception

Association of the biochemical parameters and the 4 primary taste profiles of patients with cancer were assessed to investigate the association between biochemical parameters and taste aberrations. No associations were noted between the cytokines, IL-1 β , IL-6 and any of the thresholds of the 4 tastes.

An association was noted between objectively measured bitter taste thresholds and TNF α plasma concentration. Within the cancer group, patients with lower bitter taste thresholds (bitter sensitivity increased) had significantly higher plasma levels of TNF α as compared to those patients with lower bitter taste sensitivity. In this study a high detection threshold was designated when an individual threshold of 4 was reached or not detected whereas a low threshold was designated as taste threshold concentrations 1, 2 and 3.

More specifically, for bitter detection, patients with a high threshold, that is, a low sensitivity to bitter had a mean TNF α concentration of 2.58 ± 1.85 sem pg/ml which was significantly lower ($p < 0.05$) than patients who had a heightened sensitivity to the detection of bitter taste (18.74 ± 3.42 sem pg/ml). Similar results were seen for the recognition of bitter taste where the mean TNF α concentration for patients with a high sensitivity to bitter (19.10 ± 5.4 sem pg/ml) was significantly greater ($p < 0.05$) than compared to patients with a low sensitivity to bitter recognition (11.32 ± 3.41 sem pg/ml). Although not significant, plasma levels of IL-1 β were higher in patients with heightened bitter sensitivity (Figures 7.6 and 7.7).

In addition, the relationship between serum CRP and objectively measured taste perception was investigated. With regard to bitter taste, patients with heightened bitter sensitivity (low thresholds), had significantly higher serum CRP concentration (12.9 ± 1.58 sem mg/l) compared to patients with lower bitter sensitivity thresholds (5.44 ± 1.54 sem mg/l). No differences were noted between the recognition of bitter taste perception. Analysis of the other tastes, namely, sweet, sour and salt revealed no association with cytokines or with the associated inflammatory response denoted by an elevated serum CRP.

Based on the above information, the null hypothesis is rejected and the following hypothesis is accepted:

There is a relationship between heightened bitter taste perception and elevated levels of plasma cytokine, $TNF\alpha$ and production of the associated acute phase protein, CRP.

Table 7.2 Bitter detection and recognition thresholds and plasma TNF α level

		Plasma TNF α pg/ml	
		mean \pm sem	range
Bitter Detection	High Threshold n=11	2.58 \pm 1.85	0 *- 15.31
p<0.05	Low Threshold n=24	18.74 \pm 3.24	1.18- 42.38
Bitter Recognition	High Threshold n=13	11.32 \pm 3.41	0 *- 30.62
p<0.05	Low Threshold n=22	19.10 \pm 5.4	0 *- 42.38

* Plasma levels not detected

Table 7.3 Bitter detection and recognition thresholds and serum CRP level

		Serum CRP mg/l	
		mean \pm sem	range
Bitter Detection	High Threshold n=11	12.92 \pm 1.58	8.1 - 17.4
p<0.05	Low Threshold n=24	5.44 \pm 1.54	<1.5 - 12.2
Bitter Recognition	High Threshold n=13	9.91 \pm 1.57	<1.5 - 17.4
NS	Low Threshold n=22	6.52 \pm 1.53	<1.5 - 12.2

NS = Not significant

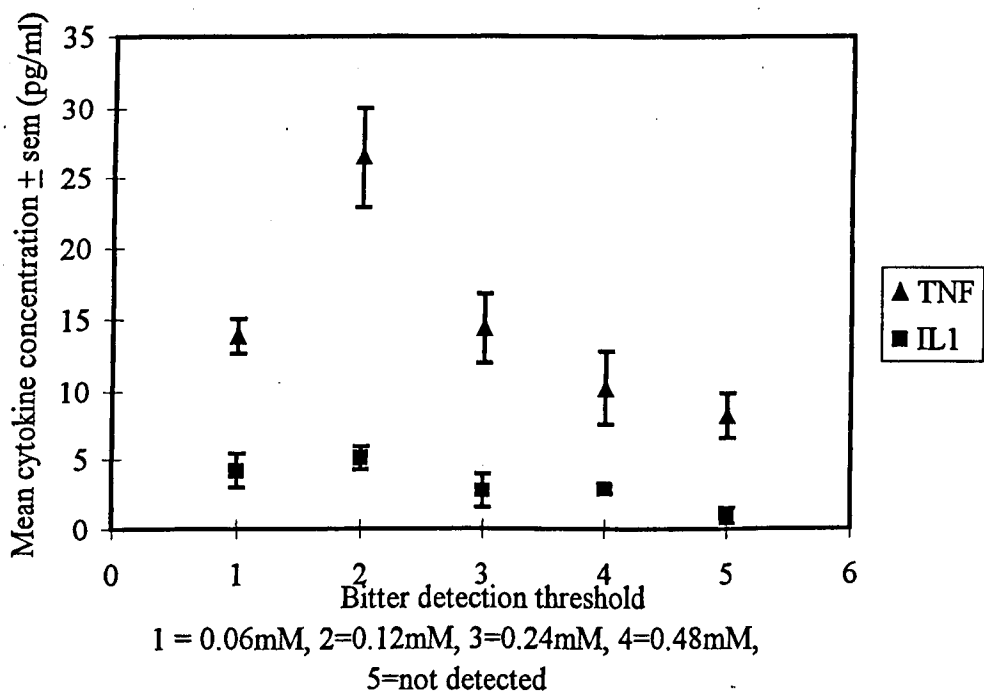


Figure 7.6 TNF alpha, IL-1 beta and bitter detection

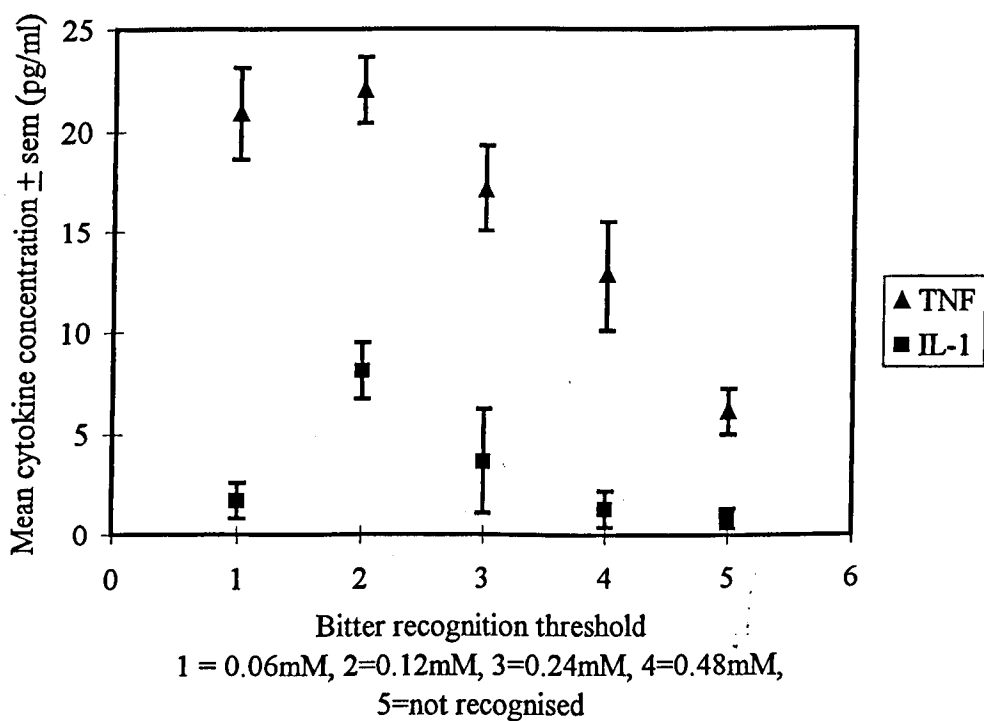


Figure 7.7 TNF alpha, IL-1 beta and bitter

7.3 Discussion

7.3.1 Cytokine production and associated acute phase response

Cytokine levels ranged from not detectable in plasma to above normal elevated levels in the assay. Interestingly albumin concentration of cancer patients were within normal levels for a healthy population. With respect to CRP, this study has shown that one quarter of advanced cancer patients (9 out of 37) exhibited an elevated CRP ($>10\text{mg/l}$) in the presence of normal albumin levels which is indicative of an ongoing inflammatory response. In addition, $\text{TNF}\alpha$ was correlated with CRP and IL-6 concentration. Likewise, an inflammatory response correlated with IL-6 concentrations. However, no such association was noted between IL- 1β and CRP concentrations.

These results support the association between cytokines and the inflammatory response denoted by elevated CRP. McMillan and colleagues in 1995 also suggested that the acute phase response was the basis of specific host immune response induced by the presence of a tumour. It is important to note that McMillan and colleagues designated a CRP concentration of $>5\text{mg/l}$ as a marker of an acute phase response whereas, in this current study, a concentration of $>10\text{mg/l}$ was used. Therefore, in this current study, the classification adopted by McMillan, although not commonly used, would have resulted in a greater number of patients classified as having an inflammatory response. Fearon and colleagues (1994) suggested that changes in hepatic protein synthesis (increase in acute phase protein production) might be mediated by IL-6. It is important to note that $\text{TNF}\alpha$ is a known mediator of IL-6 and subsequent CRP production.

The detection of TNF α in plasma has been controversial (Balkwill *et al*, 1987). In this current study, in order to minimise errors in ELISA technique, samples were analysed in one batch. Blood letting was performed under the same conditions at the same time of the day. Standardisation of this technique therefore allowed comparisons to be made within this current group of cancer patients.

7.3.2 Cytokines and dietary intake

Within the cancer group, a correlation was noted between plasma IL-6 concentrations and that of dietary fat and carbohydrate intake. Patients with elevated IL-6 concentrations demonstrated significantly higher fat intakes and lower carbohydrate intakes as compared to patients with lower plasma IL-6 concentrations. Although a correlation was noted between TNF α and IL-6, no association was noted between TNF α and any dietary intake. It is tempting to speculate that increased IL-6 may be caused by higher dietary fat intakes. The host cytokine response exhibited in this study requires arachidonic acid derived from dietary sources (Calder, 1996). With lower fat intakes, the percentage of carbohydrate intake may predominate and may subsequently attenuate IL-6 production, an important mediator of the inflammatory response. This is of particular interest as these results suggesting that cytokine production may influence dietary intake. These results also highlight the role that cytokines may play in taste perception associated with advanced malignancy.

7.3.3 Bitter taste perception and cytokine production

The association between cytokine production, the associated inflammatory response and taste perception profiles were investigated. Patients who demonstrated an elevated TNF α were found to have increased ability to detect and recognise bitter taste. A similar association was noted between bitter detection thresholds and CRP. This suggests that patients with increased sensitivity to bitter had elevated TNF α levels. This was particularly important as patients with heightened bitter sensitivity noted changes in this taste modality. No association between cytokines and any of the other tastes namely, sweet, sour and salt were noted.

These findings have not previously been noted in cancer patients. It is of great importance in light of the heightened bitter taste noted in the cancer patients and the impact of this phenomenon on dietary intake, food preferences and QOL highlighted in previous chapters.

These results suggest that higher plasma concentrations of TNF α may be responsible for an alteration in bitter taste perception noted in these cancer patients. In addition, the inflammatory response associated with TNF α has been associated with bitter taste aberration. There is recent electrophysiological evidence to suggest that cytokines may influence changes in the neurological pathways that mediate taste information.

7.3.4 Cytokines and neural pathways

It has previously been demonstrated that cytokines modulate neural activity via the activation of vagal afferents. Much of the recent published evidence examining the causes of altered taste perception suggests that afferent neural pathways are sensitised. These connections project taste information into the brain stem from the taste receptor cells (Hermann *et al*, 1983). Niiijima and Meguid (1995) demonstrated that cytokines might activate gastro-intestinal afferents, thereby enhancing neuronal sensation by increasing the level of activity in nerves relaying information from peripheral nerve to brain.

The results highlighted in this chapter support recent evidence of the association between cytokine production, inflammatory response and altered taste perception. This may explain the change in bitter perception that is modulated at cellular level (Kinnamon and Getchell, 1991). In a similar manner to visceral sensation, taste impulses reach the brain stem via the chorda tympani and are interpreted in the brain. Electrophysiological evidence from recordings taken from the tympani following lipolysaccharide (LPS) administration, suggest that products of immune cells modulate peripheral gustatory system (Phillips and Hill, 1996). Injection of LPS in animals mimics the profile of the inflammatory response in man. It can therefore, be speculated that at this level, the observed alterations in bitter taste may occur.

Taste responses are often observed when blood concentrations are low and therefore a neuronal route mediated by cytokines in local tissue may explain the mechanism of action. This was reported by Goehler and colleagues (1995) who demonstrated induced taste

aversions and anorexia were reversed following subdiaphragmatic vagotomy in animal studies. Increased production of IL-1 β was associated with an increased activity of vagal afferents. This work contributed further to the knowledge that cytokines are key messengers in the immune to brain signalling. IL-1 β centrally mediated response effects are blocked by peripherally administered IL-1 β antagonists, suggesting that there is a critical involvement of peripheral IL-1 receptors. In addition, centrally mediated illness responses are blocked by vagotomy, suggesting that IL-1 β directly or indirectly activate vagal afferents. The basis for the intervention study reported in the following chapter is based on the theory that an attenuation of the inflammatory response may influence bitter taste sensitivity and have a positive effect in food selection.

8.1 Introduction

8.1.1 Intervention with omega 3 fatty acids

This chapter evaluates the impact of intervention aimed at minimising altered taste perception. The rationale for the use of this intervention is based on results highlighted in the previous chapters. The association between cytokine production, associated inflammatory response and alterations in bitter taste perception have been highlighted in chapter 7.

Recent studies have demonstrated the use of anti-inflammatories and immunosuppressive mediators in regulating cytokine production (Tilg *et al*, 1997). The use of pharmacological intervention in studies in the palliative care setting is limited due to ethical considerations. More appropriate intervention is based on novel nutritional substrates intervention aimed at ameliorating the acute phase response that may also have a positive effects on other nutritional symptoms associated with taste perception such as weight loss (Wigmore *et al*, 1996).

It is established that dietary omega 3 fatty acids may modify inflammation (Sanders 1993). The inhibition of pro-inflammatory cytokines by omega 3 fatty acids may be a consequence of the direct inhibiting activity of the eicosanoids namely, prostaglandins of the 3 series. One of the main precursors of the eicosanoid 3 series is arachidonic acid. It is thought that omega 3 fatty acids reduce arachidonic metabolites potentially involved in inflammatory processes resulting in the production of less active 2 series prostaglandins. Alternatively, the omega 3 fatty acid, eicosapentanoic acid EPA, may replace the

membrane uptake of arachidonic acid, competing for incorporation into leucocyte cell membrane.

Considering the results to date and that of the pharmacological effects of omega 3 fatty acids inhibiting cytokine production, the following intervention study was conducted. To date, no such intervention has been conducted within the hospice setting with patients with advanced cancer.

8.1.2 Aims of the study

The aims of this study are:

- i. To down-regulate the cytokine production and the associated inflammatory response.
- ii. To evaluate the effect of omega 3 fatty acid intervention on taste perception in patients with advanced cancer.
- iii. To evaluate the implementation of intervention in patients with advanced cancer in the hospice setting, acceptable to both staff and patients.

8.2 Methods

8.2.1 Sample group

Patients with advanced cancer were recruited from St.Columba's Hospice, Edinburgh. Previous studies that have used omega 3 fatty acid intervention indicate that 20 patients would allow analysis to 5% statistical significance (Wigmore *et al*, 1996). Based on recruitment response reported in chapter 3, it was estimated that approximately 30 patients recruited would obtain 20 subjects for analysis, allowing a drop-out rate of 33%.

More clinically stable patients were recruited at the discretion of the medical and nursing staff. In an attempt to characterise effects of omega 3 fatty acid supplements, outcome measures were compared to baseline. To assess any differences accountable to the intervention used, an appropriate control group would receive an iso-energetic quantity of fatty acids (placebo) without disturbing the ratio of n-3 to n-6 fatty acids present in their baseline. However, in palliative care, a placebo controlled study was considered unethical.

Inclusion Criteria

- i. Patients admitted to St.Columba's Hospice, Edinburgh with a diagnosis of cancer.
No specific cancer types were excluded from the study.
- ii. Day Hospice patients. Ethical approval was obtained to allow the recruitment of

patients from the Day Hospice centre to enable the generation of a wider sample population.

Exclusion criteria

- i. Patients currently or six weeks after receiving chemotherapy, radiotherapy or drug treatment for oral candidiasis were excluded from the study as these treatments are known to have a significant effect on taste perception.

Patients were free to discontinue their participation in the study at any time. In addition, the development of any adverse side-effects of the intervention excluded subjects from continuing in the study. Any subject whose condition deteriorated significantly or developed additional uncontrolled symptoms were also excluded. Throughout the study, information regarding the reasons for discontinuation were noted.

8.2.2 Ethical issues

Ethical approval was granted from the Medical and Oncology Ethics committee, Lothian Health Board, for this intervention study (Appendix 1). In addition to procedures outlined in chapter 2, approval was granted to:

- i. Administer a specific dose of omega 3 fatty acid intervention to a group of patients with advanced cancer.
- ii. Obtain blood samples solely for the purposes of research to allow the

accurate timing of blood letting according to the schedule of assessments.

- iii. Include Day Hospice patients. Patients who attended the Day hospice on a regular basis were considered for inclusion to the study.

Informed consent was obtained from all patients before conducting any study related procedure (Appendix 3 and 4). Patients were given adequate verbal and written information about the nature and purpose of the study and the opportunity to ask questions. After having received study information, patients were allowed at least a 24 hour period, before consenting to participate. As outlined in the consent forms, subjects could not expect to derive any benefit from the intervention.

8.2.3 Intervention

Intervention focused on the use of omega 3 fatty acids. A highly concentrated marine fish oil in tryglyceride form, *Pikazol*, (Lube plc., Denmark) in the form of 0.5g capsules were provided. In fulfilment of the Medicines Act 1968, approval to conduct this research (clinical trials exemption certificate) was sought from the licensing authority (Medicine Controls Agency, Department of Health; Appendix 2).

Description of intervention product

Name:	Pikazol®
Composition:	65% long Chain fatty Acids

of which 33% eicosapentanoic acid, 27% docosahexaenoic acid

Other ingredients: Vitamin A (<1 I.U. / g n-3)

Vitamin D (<1 I.U. / g n-3)

Vitamin E (4.4 I.U. / g n-3)

Dosage: 6g / day for 4 weeks

Manufacturer: Lube A/S plc., Denmark

Pikazol® (Lube plc.) fish oil supplements, have previously been used in a number of clinical trials (Christensen *et al*, 1996; Olsen *et al*, 1992). More recently, *Pikazol®* has been used in a multi-center trial in pregnant women with pre-eclampsia, pregnancy induced hypertension, previous intrauterine growth retardation and chronic hypertension (Salvig *et al*, 1996).

Dosage

Supplementation of 6g fish oil per day is considered non-toxic and not associated with any side-effects (Olsen *et al*, 1992; Salvig *et al*, 1996). However, as in the ingestion of any kind of oil, loose stools may be a consequence of ingestion. The dose of *pikazol* was achieved using the incremental method, that is, the daily dose gradually increased over the first week to the recommended dose as follows.

Day	No. Capsules Consumed	EPA
1	2 (1g fish oil)	0.33g
2	4 (2g fish oil)	0.66g
3	6 (3g fish oil)	0.99g
4	8 (4g fish oil)	1.32g
5	10 (5g fish oil)	1.65g
6 onwards	12 (6g fish oil)	1.98g

8.2.4 Intervention study outcomes

The following assessments were made at baseline and following 4 weeks of supplementation. In a longitudinal study, where the influence of a disease or nutritional intervention in malnourished patients may lead to subtle changes in composition, accurate and precise measurements are required. Chapters 1 and 2 provide a fuller account of the use of the following assessment tools used in patients with in advanced cancer.

Taste Perception

Detection and recognition thresholds for the taste qualities of salt, sweet, sour and bitter were objectively determined for each patient using the International Standard for Sensory Appraisal. The repeatability of the measures of taste perception assessment has previously been addressed in chapter 2. In addition, patients were asked about their perception of taste sensitivity and of any changes that they have noticed during their illness.

Assessment of body composition

Nutritional assessment was performed on all subjects using upper arm anthropometry (skinfold thickness, arm muscle circumference), weight and hand-grip dynamometry. These tools have previously been used in longitudinal studies (Wigmore *et al*, 1997). Measurements at baseline and following intervention were taken by the same trained observer to reduce any errors (Walker and Kindlen, 1988).

QOL assessment

In this study, the efficacy of intervention was measured by its ability to modify the subjective parameter, namely, QOL. The influence of sensory aberrations on QOL was assessed during a semi-structured interview technique. The semi-structured interview, based on the HAD scale, has been shown to accurately identify changes in QOL over time (Zigmond and Snaith, 1983).

Blood Parameters

Analysis was performed on blood samples taken from recruited subjects at baseline and following intervention. Plasma levels of cytokines (TNF α , IL1 β and IL6), serum CRP and serum albumin were assessed as described in chapter 2. Plasma levels of ω -3 fatty acids were measured after total lipid extraction by capillary gas chromatography to assess the amount of fatty acid uptake (Wilson *et al*, 1992). Plasma fatty acid composition has been

shown to be good indicator of the habitual intake of dietary fat (Folsom *et al*, 1995). In this study by Folsom and colleagues, fat intake measured using a food frequency questionnaire correlated with plasma fatty acid composition.

Medical status

Assessment of symptoms, drug regimens and any subsequent changes were reviewed and recorded at baseline and thereafter at weekly intervals or when significant changes occurred, until the end of the intervention period.

Dietary intake

A subjective assessment of food intake was constructed, based on a tool used to quantify food intake in longitudinal studies (Corlio *et al*, 1992). This tool was designed to measure individual changes in dietary intake from baseline perception. Based on a visual analogue scale, patients choose one of five key words to describe their food intake as compared to normal (very little, little, normal, nothing, a lot). 'Normal' indicates no change compared to what was consumed before illness. In comparison, 'a lot' describes food intake that is superior to what was consumed before illness. Similar structured visual analogue scales have been used by Willcox and colleagues (1984) to measure subjective responses related to appetite, nausea and mood in patients with advanced cancer.

8.2.5 Schedule of assessments

Study parameters were measured at baseline and following the intervention period (4 weeks), using the following schematic representation of study procedures:

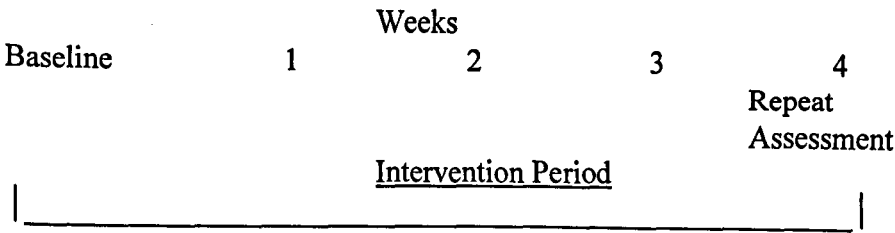


Figure 1 Time Scale

During the Study, the following measurements were taken as follows:

	Baseline	Week			End of intervention
Week	0	1	2	3	4
Informed Consent	x				
Demography	x				
Medication Check	x	x	x	x	x
Medical Status	x	x	x	x	x
Compliance		x	x	x	x
Diary Check (Day Hospice)		x	x	x	x
Taste perception	x				x
Blood Samples	x				x
QOL	x				x
Anthropometry	x				x
Dietary Intake	x				x
Intervention	x ¹	x	x	x	x ²

¹. Commenced following baseline assessments

². Stopped prior to assessment performed following intervention period

8.2.6. Compliance

Throughout the study, monitoring of patient progress and compliance was required. On the ward, compliance was maximised by administering supplements as part of daily drug rounds (Appendix 9). At maximum dosage, patients received 12 x 0.5g capsules either as 3 capsules q.d.s or 4 capsules t.i.d. Two patients requested their prescription at mealtimes.

Patients recruited from the Day Hospice were given diaries that highlighted the incremental dosage during the first week (Appendix 10). Subjects used this diary to record the number of capsules consumed daily, reasons for not meeting the required dosage if applicable and any side-effects observed. The diary was checked by the researcher weekly and any issues regarding compliance and any side effects recorded and discussed with the patient. Fortnightly supplies of supplements were given to the Day Hospice patients.

Compliance of in-patients was effectively monitored by medical and nursing staff. Day hospice staff played an additional role in checking compliance during weekly visits. In addition, compliance was checked by measuring the plasma uptake of n-3 fatty acids and hence the incorporation of n-3 fatty acids in plasma cell membrane (total lipid extraction by capillary gas chromatography, Wilson *et al*, 1992).

To summarise, throughout the intervention period the following were monitored:

1. Consumption of capsules.
2. Side effects of consumption of fish oil capsules.
3. Acceptability of dosage of supplements to subjects.
4. Bowel habits.

5. Any possible reasons for non-compliance

8.3 Results

8.3.1 Demographic data

Twenty two patients (12 Male, 10 Female) with advanced cancer were recruited to the intervention study, representing 12% of all in-patient admissions within the 7 month recruitment period. Mean age was $76.5 \pm 8.2\text{sem}$ (range 57-89) years. Table 8.1 highlights the primary diagnosis of patients of which more than half (54%, n 12) had diagnosed metastatic disease.

Of the 22 enrolled patients, just over one quarter (n 6; 4 Male, 2 Female) completed the supplementation trial (Table 8.2). The mean age of this sub-set of patients was $72 \pm 4.3\text{sem}$ (range 58-84) years. Of the six patients who completed the intervention trial, two were recruited from the Day Hospice. The demographic characteristics and reasons for non-completion of the remaining 16 patients are highlighted in table 8.3

Table 8.1 Primary diagnosis of cancer patients enrolled to the intervention study

Primary Diagnosis	Number of Patients n 22	%
Lung	4	18
Prostate	4	18
Colon	3	14
Rectum	2	9
Ovary	1	4
Unknown	3	14
Other	5	23

**Table 8.2 Demographic characteristics of patients who completed the
intervention study**

Patient	Age	Sex	Diagnosis	Metastatic Disease	Length of admission (days)	Reasons For Admission to Hospice
01	78	M	Stomach	Bone	Day Hospice	N/A
02	61	M	Prostate		123	Continuing Care
03	67	M	Liver	Bone	92	Continuing Care
04	78	F	Mengioma		Day Hospice	N/A
05	84	F	Ovarian		56	Symptom Control
06	58	M	Lung		36	Continuing Care

Table 8.3 Reasons for withdrawal from the intervention study following baseline assessment

Age	Sex	Primary Diagnosis	Metastatic Disease	Reason For Admission	Length of Stay (days)
Reason: Clinical condition deteriorated					
89	F	Unknown	Lung	Pain Control	29 ^{1.}
88	M	Prostate		Continuing Care	22 ^{1.}
76	M	Prostate	Liver	Day Hospice	N/A ^{1.}
66	M	Prostate	Bone	Pain Control	11 ^{1.}
82	M	Colon	Liver	Respite	14 ^{1.}
68	M	Unknown		Respite	55 ^{1.}
65	F	Unknown	Liver	Continuing Care	5 ^{3.}
57	M	Colon	Liver, Bladder	Continuing Care	21 ^{3.}
80	F	Bronchus		Pain Control	9 ^{1.}
Reason: Too many supplements to take					
79	M	Rectum		Symptom Control	28 ^{2.}
87	F	Ovary		Symptom Control	21 ^{2.}
78	M	Myeloma		Day Hospice	N/A ^{2.}
77	F	Bronchus		Day Hospice	N/A ^{3.}
Reason: Patient changed their mind					
89	F	Rectum	Liver	Symptom Control	14 ^{1.}
Reason: Supplement Aggravated Colostomy					
76	F	Colon	Brain	Day Hospice	N/A ^{2.}
Reason: Cataract Operation					
87	M	Bronchus	Liver	Respite	32 days ^{1.}

¹ **Withdrawn after baseline assessments performed**

² **Took supplements for 7 days before withdrawing from study**

³ **Took supplements for 14 days before withdrawing from study**

8.3.2 Gustatory and olfactory perception profiles

Baseline profiles

Baseline assessment of taste perception was performed on all subjects (n 22) and compared with profiles of the age matched control group reported in chapter 3. A significant difference was noted between the cancer and control groups for bitter taste detection ($p<0.05$; Figure 8.1). Patients with advanced cancer had a significantly lower threshold for bitter detection compared to control subjects, indicating an increased ability to detect bitter taste perception. No other differences in taste detection and recognition profiles for sweet, salt and sour were noted between the cancer and control groups.

Profiles following intervention

Of the patients who completed the intervention period, comparisons were made between baseline assessments and post-supplementation taste profiles (Table 8.4). No pattern of changes of taste profiles were noted following supplementation.

Likewise, objective assessment of olfactory perception revealed no difference in the number of odours identified following four weeks supplementation (table 8.5).

Subjective assessment of gustatory and olfactory perception

However, patients noted changes in their taste perception as described below.

Patient 01: 78year old Male, Stomach Cancer with Bone metastases

Prior to baseline assessments, a change in taste perception was reported for several weeks. Gustatory changes encompassed a blunting of sweet perception coupled with a blunting of olfactory perception. No changes in taste and smell perception were reported following supplementation.

Patient 02: 61 year old Male, Prostate cancer

Both a heightened bitter taste coupled with a blunting of taste perception was reported at baseline. Following supplementation, subjective experiences of bitter taste were less noticeable. This is in contrast to the objective measurement of bitter perception in which detection thresholds were lowered following supplementation, indicating a heightened bitter taste perception.

Patient 03: 67 year old Male, liver cancer with Bone metastases

At baseline, a blunting of taste perception was reported. This was not specific to any taste modality but was reported as a reduction of the pleasurable aspect of a variety of food items such as sweet foods and fruit. Following 4 weeks supplementation of omega 3 fatty acids, improvements in the blunting of taste was reported. No changes in olfactory perception were objectively and subjectively measured throughout the intervention period.

Patient 04: 78 year old Female, Meningioma

A loss of taste perception, reported at baseline, was unchanged following supplementation.

No changes of olfactory perception were noted throughout the study.

Patient 05: 84 year old Female, Cervical cancer

A slight blunting of taste perception reported at baseline remained following 4 weeks supplementation. This was coupled with a blunting of olfactory perception throughout the study period.

Patient 06: 58 year Male, Lung cancer

A blunting of taste perception and an increased sweet perception, first noticed at diagnosis was reported throughout the study period.

In addition to alterations in taste perception, other symptoms experienced by subjects are summarised in the table 8.

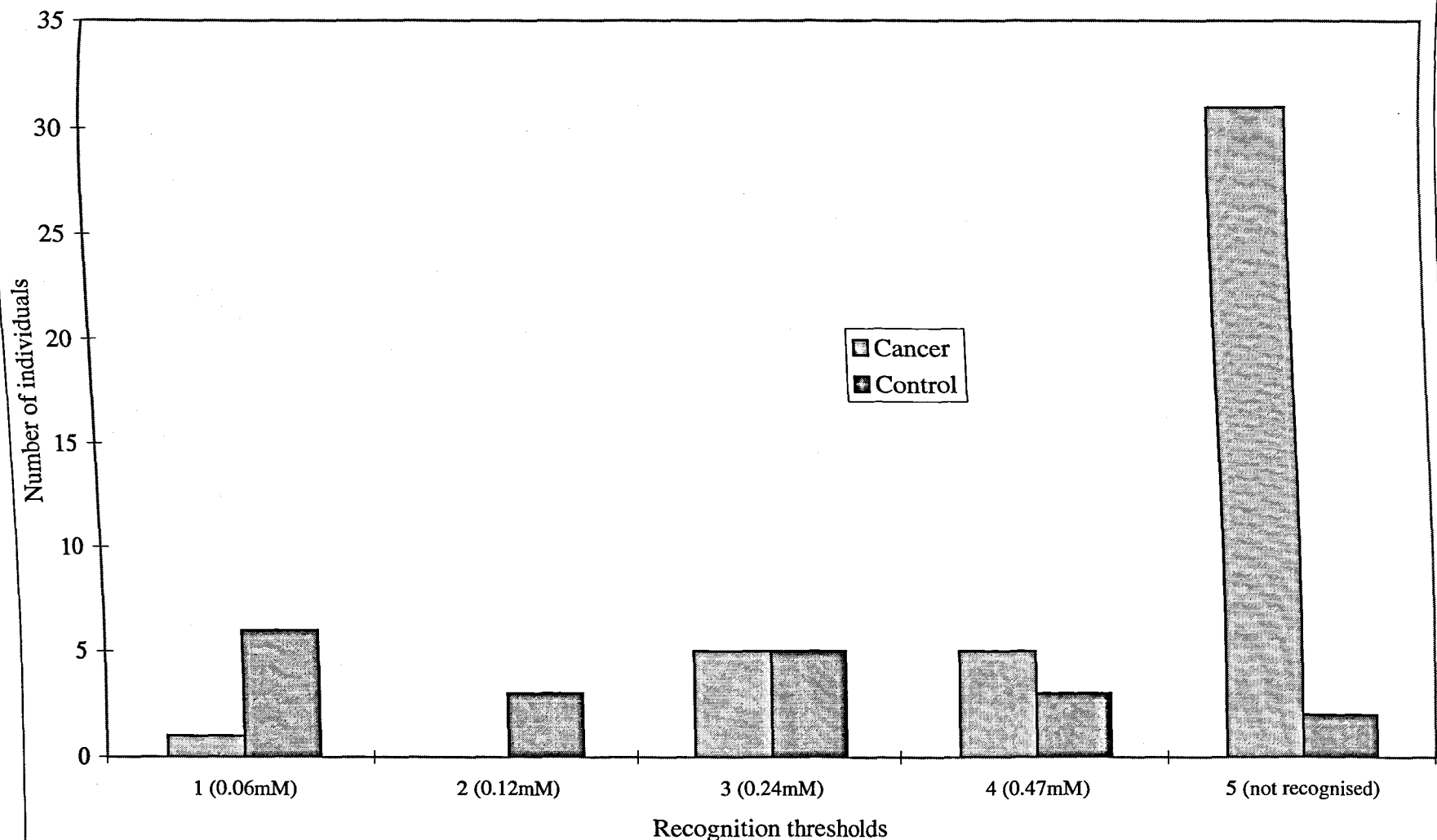


Figure 8.1 Comparison of bitter perception profiles of cancer patients and control subjects

Table 8.4 Taste perception profiles before and after 4 weeks supplementation with omega 3 fatty acids

Taste	Assessment Period	Patient					
		01	02	03	04	05	06
		Thresholds Value					
Sweet Detection	Baseline	4	5	3	5	5	2
	Post Supplementation	1	4	1	5	5	2
	Change in threshold	↓	↓	↓	N	N	N
Sweet Recognition	Baseline	4	5	4	5	5	3
	Post Supplementation	3	4	2	5	5	2
	Change in threshold	↓	↓	↓	N	N	↓
Sour Detection	Baseline	1	1	1	2	1	1
	Post Supplementation	4	3	2	1	2	2
	Change in threshold	↑	↑	↑	↓	↑	↑
Sour Recognition	Baseline	5	1	2	4	2	2
	Post Supplementation	5	3	3	2	4	3
	Change in threshold	N	↑	↑	↓	↑	↑
Salt Detection	Baseline	1	2	4	1	4	3
	Post Supplementation	3	4	1	3	1	3
	Change in threshold	↑	↑	↓	↑	↓	N
Salt Recognition	Baseline	4	2	4	4	4	4
	Post Supplementation	5	4	5	5	4	4
	Change in threshold	↑	↑	↑	↑	N	N
Bitter Detection	Baseline	3	1	4	4	5	3
	Post Supplementation	4	5	2	2	3	4
	Change in threshold	↑	↑	↓	↓	↓	↑
Bitter Recognition	Baseline	5	1	4	5	5	3
	Post Supplementation	4	5	4	5	5	4
	Change in threshold	↓	↑	N	N	N	↑

N= No Change in threshold following supplementation

↑ = Increase in threshold following supplementation (decreased taste sensitivity)

↓ = Decrease in threshold following supplementation (increased taste sensitivity)

Table 8.5 Olfactory perception at baseline and post-supplementation

Patient	Number of Odours Recognised (Total no. assessed = 10)	
	Baseline	Post-Supplementation
01	5	5
02	6	5
03	5	4
04	6	5
05	7	6
06	6	7

Table 8.6 Symptoms reported by subjects at baseline and post supplementation

Oral and Gastrointestinal symptoms reported by patients		
Patient	Baseline	Post Supplementation
01	Appetite loss Nausea Constipation Diarrhoea Dry mouth	Nausea Diarrhoea Dry Mouth ¹
02	Appetite loss Nausea Dry Mouth Pain	Appetite loss Dry Mouth ¹
03	Diarrhoea Dry Mouth	Diarrhoea ¹ Dry Mouth ¹ Nausea
04	Dry Mouth	Dry Mouth ² Pain Constipation
05	Pain	Dry Mouth
06	Nausea Constipation Dry Mouth	Less Nausea Constipation ²

¹ Increased intensity of symptom from baseline

² Decreased intensity of symptom from baseline

8.3.3 Impact of altered taste perception on QOL

Baseline assessment of QOL

A baseline assessment of the impact of altered taste perception on the QOL of patients was made in all patients who reported a change in chemosensory perception (n 18, 82%). The following responses mirror those obtained from the previous group of patients with advanced cancer reported in chapter 4.

Of these 18 patients, one half of the group first observed altered taste perception at diagnosis and the remainder during the months before questioning. With regards to the impact on eating habits, sixteen patients (89%) reported that taste changes reduced the amount of food they consumed and five patients (27%) reported that the presence of altered taste perception, altered their selection of food items. Individual responses are highlighted below:

"I eat because I know I must and that I need to....like I take a walk because I know it is good for me"

(Male, 78 years, Myeloma)

The question 'Have the taste changes affected your general enjoyment of life?' was asked. Half of respondents (n 8) reported that taste changes had no effect on their enjoyment of life:

"I have lost my taste and that is that.....I get enough enjoyment still out of my food".

(Female, 85 years, Ovarian Cancer)

However, for the remaining patients, taste changes had a negative effect on everyday life. This was related to family concerns about a poor appetite and a general enjoyment of food. More than half of the respondents (n 15) reported that their taste changes affected those close to them. Nine patients associated weight loss with a lack of interest in their appearance.

Impact of taste changes on QOL following intervention

Patient 01: During the semi-structured interview, a reduced appetite was directly attributed to a change in taste perception. Despite feeling frequently hungry, the taste of food reduced the desire to eat. This phenomenon appeared to have an impact on the choice of food but no impact on the general enjoyment of life. Other aspects of everyday life remained unchanged as the patient continued to enjoy certain hobbies. However, a loss of appetite and a change in taste perception had become a major worry for the patients main carer who was involved in food preparation.

Patient 02: Altered taste perception was reported as a symptom continuously experienced. From analysis of the semi-structured interview, altered taste perception affected food selection and was reported as having a negative impact on his enjoyment of life. Moreover, weight loss was reported as a negative impact on everyday life.

Patient 03: Positive responses towards aspects of everyday life that included enjoying socialising and hobbies were noted. This did not change throughout the study period.

Patient 04: In general, positive responses to questions regarding everyday life were noted at baseline and following intervention.

Patient 05: Changes in taste perception were reported as a predominant symptom. A significant amount of weight loss during the illness had a distinct impact on everyday life:

'I get a fright when I look in the mirror cause I've lost so much weight'

Patient 06: A change in taste perception at baseline was reported as an important cause of reduced food intake and influencing food selection. This was reported as impinging on QOL.

"They (family) ask if I am eating...They worry that I don't eat and that I'm losing weight"
(Female, 78year, Lung Cancer)

8.3.4. Anthropometric parameters

Anthropometric changes following supplementation

Anthropometric status was assessed at baseline and following the supplementation period using indices of upper arm anthropometry (TSF, AMC). Following supplementation, comparison with baseline measurements are shown in table 8.7.

All six patients at baseline were weight losing which was present for at least several weeks during the later stages of their illness. However, following 4 weeks supplementation, an increased weight was noted in four patients (1-4kg) and one patient continued to lose weight but at a reduced rate (Figure 8.2). No measurement of weight was made in one bed-bound patient. In addition, changes in triceps skinfold thickness are shown in Figure 8.3.

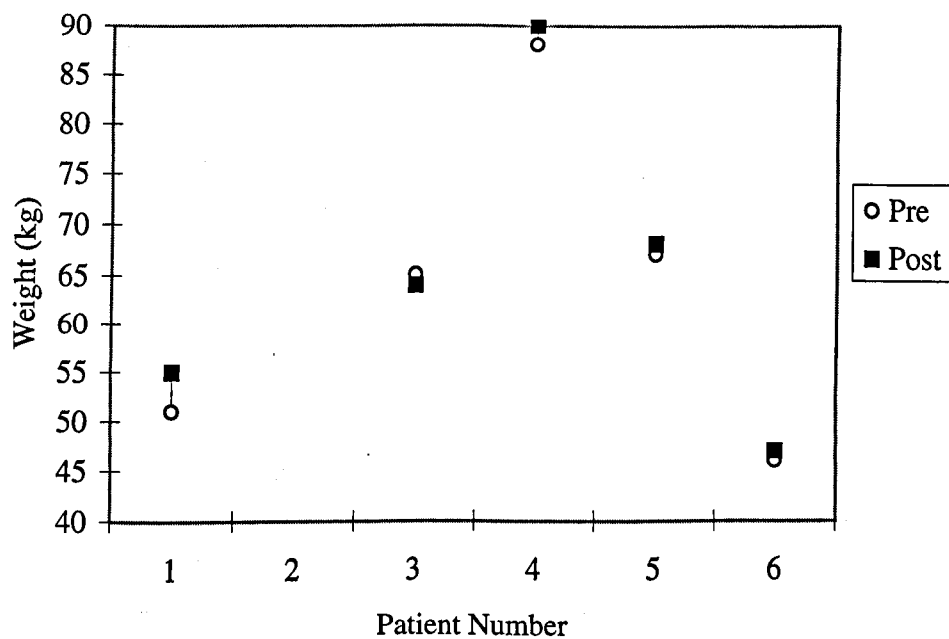


Figure 8.2 Changes in weight of cancer patients following intervention

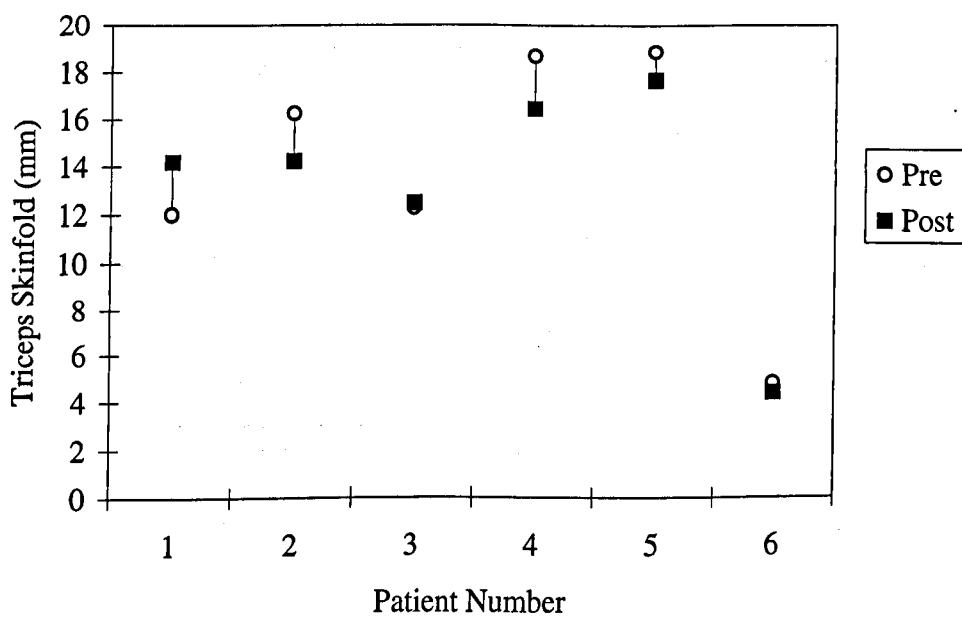


Figure 8.3 Changes in TFS following intervention

**Table 8.7 Anthropometric changes following 4 weeks supplementation with
omega 3 fatty acids**

Anthropometric Parameter		Mean	± sem	Range
Weight (kg)	Baseline	63.4	7.3	46-88
	Post Supplementation	64.8	7.3	47-90
Hand Grip (kg)	Baseline	11.3	1.9	6-20
	Post Supplementation	13.7	1.6	10-20
TSF (mm)	Baseline	13.8	2.2	4.8-18.8
	Post Supplementation	13.2	1.9	4.4-17.6
TSF *	Baseline	88.8	15.5	68.6-109
	Post Supplementation	79.3	15.3	63-103
AMC (mm)	Baseline	22.0	0.8	18.7-24.2
	Post Supplementation	21.8	1.5	16.9-26.9
AMC*	Baseline	91.1	3.4	92.7-106.0
	Post Supplementation	88.8	6.1	84-118
AMA (cm²)	Baseline	386.5	27.7	279.2-464.7
	Post Supplementation	388.6	52.7	228.4-573.9
AMA *	Baseline	81.3	7.0	84.7-13.3
	Post Supplementation	81.3	13.5	69-15.1

* Expressed as a percentage of reference values (Lehmann *et al*, 1991; Burr and Phillips, 1993)

8.3.5 Impact of altered taste perception on food selection

Patients were asked to describe their current dietary intake. The following question was asked 'How would you describe your usual food intake?'. Responses were categorised by patients into one of five categories (very little, little, normal, nothing, a lot; Table 8.8).

Patient 01: At baseline, the negative impact of altered taste perception on appetite and food selection was reported. A loss of sweet perception noted at baseline was reflected in the avoidance of certain sweet tasting foods. Food intake was reported as less than usual throughout the study period.

Patient 02: Dietary intake was, at baseline, described as less than usual but further decreased during the intervention period. At baseline, foods items such as potatoes and red meat were reported to have a bitter taste. This was coupled with a heightened bitter taste perception at baseline.

Patient 03: A reduced appetite and altered food preferences were attributed to alterations in taste perception. At baseline, although little solid food was consumed, this was reported as more than usual intake. Dietary intake was reduced further following supplementation.

Patient 04: No change in dietary intake was reported throughout the supplementation period. Altered taste perception appeared to have a greater impact on food selection although no foods were reported (table 8.8).

Patient 05: Altered taste perception appeared to have no impact on food selection. At baseline, dietary intake was described as less than usual which increased to more than usual following the supplementation period. This did not influence appetite or the enjoyment of food.

Patient 06: Altered taste perception was reported as an important cause of a reduced appetite and influencing food selection. In the latter stages of the illness, patient experienced early satiety .

**Table 8.8 Subjective description of dietary intake at baseline and post
supplementation**

Patient	Baseline	Post Supplementation
01	Less than usual	Further Decrease Little solid food
02	Less than usual	Further Decrease Very Little of Anything
03	More than usual Little solid food	Less than usual Very little of anything
04	Less than usual	Unchanged
05	Less than usual	More than usual
06	Less than usual Little solid food	Unchanged

8.3.6 Biochemical parameters

The cytokines, IL1 β , TNF α and IL-6 were measured in six patients at baseline and following four weeks supplementation with omega 3 fatty acids. Plasma levels of TNF α in all six patients were found to be less than 15.6 pg/ml. The changes in IL1 β and IL-6 are shown in the table 8.9. Levels of IL-1 β increased in three patients and decreased in the remaining three. Likewise, levels of IL-6 had decreased in only one patient but only slightly increased in four patients.

Table 8.9 **Changes in cytokine levels following supplementation**

Plasma IL-1 β pg/ml			Plasma IL-6 pg/ml	
Patient	Baseline	Post-Supplementation	Baseline	Post-Supplementation
01	41	43	11	32
02	41	42	26	29.4
03	80	46	27.5	27.5
04	46	43	1.0	1.0
05	56	53	26	15.0
06	46	48	20	33

8.3.7 Compliance

Compliance was assessed by the plasma uptake and incorporation in the cell membrane. Following a four week supplementation period, plasma levels of EPA and DHA had increased and no pattern of change is noted with arachidonic acid in all patients (Table 8.10).

Table 8.10 Plasma fatty acid concentrations pre and post supplementation

Plasma Concentrations %						
Patient	Arachidonic Acid		EPA		DHA	
	Pre	Post	Pre	Post	Pre	Post
01	6.75	6.9	1.13	8.5	2.95	4.5
02	5.94	6.98	0.58	4.67	1.3	3.58
03	7.64	3.92	0.24	0.65	1.71	1.35
04	2.43	3.39	0.74	2.62	0.91	2.57
05	4.62	5.1	0.83	7.66	1.36	3.89
06	5.96	5.91	0.38	2.84	1.6	2.84

Pre = Baseline assessment

Post = Post-Supplementation assessment

8.3.8 Medications taken by patients in the intervention group

None of the medication regimens outlined below were known to influence taste perception.

Medication regimens remained consistent throughout the patients participation in the study.

Patient	Indication	Medication
1	Sedative	Temazepam
		Diazepam
	Analgesic	Morphine
		Naproxen
	Steroid	Prednisolone
2	Analgesic	Morphine
	Sedative	Temazepam
	Laxative	Co-danthramer
3	Analgesic	Morphine
		Diclofenac
	Anti-emetic	Metochlopramide
	Anti-diarrhoea	Lomotil
	Sedative	Temazepam
	Steroid	Dexamethasone
4	Analgesic	Paracetamol
	Asthma	Voltarol® (A&H)
		Becotide® (A&H)
5	Diuretic	Frusemide
	Anti-emetic	Domperidone
	Analgesic	Aspirin
	Ulcer-healing	Ranitidine
6	Analgesic	Diamorphine
	Anti-depressant	Amitryptilline
	Laxative	Co-danthramer

8.3.9 Recruitment

During the recruitment period, reasons for exclusion of patients were noted. 169 patients were admitted to the ward during the 5 month recruitment period. The mean length of stay was 21 days (range 1-123 days). More than one third of these patients were admitted for continuing care (37%), symptom control (30%), pain control (17%) and 16% for respite care. Within the Day Hospice, 30 patients attended during the recruitment period.

The majority (96%) of the sample population (n 155) in-patients and 75% (n 24) Day Hospice attendees were excluded from the study. For in-patients, this represented a mean hospice stay of 18 days. The main reasons for exclusion from the study are highlighted in tables 8.11 and 8.12.

Table 8.11 Reasons for exclusion of in-patients from the intervention study

Reason For Exclusion	n	%
Poor prognosis	51	33
Uncontrolled symptoms	32	21
Swallowing problems	13	8
Dementia / Confusion	9	6
Distressed patients	9	6
Not eating	7	4
Nystatin treatment	6	4
Short admission (no study follow up possible: not Day Hospice or Home Care)	6	4
Hepatitis B / C positive	6	4
Recent chemotherapy / radiotherapy	5	3
Previous subject in first stage	5	3
Non malignancy	3	2
Receiving nutritional support (gastrostomy)	2	1
Language barrier	1	1

**Table 8.12 Reasons for exclusion of Day Hospice patients from the
intervention study**

Reasons For Exclusion	Number of Patients	Percentage
Distressed patient	9	38
Recent treatment	6	25
Poor prognosis	5	21
Colostomy	3	12
Hepatitis B positive	1	4

8.4. Discussion

8.4.1 Baseline measurement of taste perception

The results obtained at baseline of 22 patients with advanced cancer support the evidence that heightened bitter taste perceptions are experienced by patients with advanced cancer. This is consistent with the results of the cross-sectional study that suggested that the changes are not related to treatment. Differences in bitter detection perception were noted in which patients with cancer had heightened bitter detection perception compared to control subjects. No other differences in the detection and recognition of the other thresholds were noted.

Of these 22 patients, 82% of respondents reported an alteration in their taste perception. This group of patients may have a higher prevalence of altered taste perception as they consented to participating in a research study that had the potential to provide benefit for a symptom that they were experiencing.

Subjective information regarding the impact of altered taste perception on QOL and food choice reflected results of the first stage of investigation where patients with altered bitter taste perception reported the avoidance of bitter tasting foods such as coffee and red meat. A change in taste perception of a certain food item resulted in the reduced intake that was not substituted by another item. Although dietary intake was not quantified, this would have a negative impact on overall dietary intake and hence nutritional status. The results of this current study emphasises the need to develop individualised approaches to the dietary

management of patients who experience alterations in their taste perception. For example, the meal menu of patients may be tailored to suit alterations in taste perception.

No consistent pattern with medication regimens and taste perception profiles were noted. Concerning nutritional symptoms, the severity and duration of these symptoms varied throughout the study period. The exact impact of pharmaceutical regimens on taste perception may be difficult to control that highlights inherent difficulty of conducting research within a dynamic group of patients in a longitudinal study.

8.4.2 Effects of omega 3 fatty acid intervention

In this current study, patients acted as their own controls, as comparisons were made between baseline and post supplementation parameters. Changes in reported taste perception were noted following intervention where two of six patients reported an improvement in their taste perception. One patient reported a heightened bitter taste at baseline that was less noticeable following supplementation. This was reflected in the objective measurement of bitter thresholds in which bitter perception was detected and recognised at a lower concentration at baseline compared to following intervention. This suggests that objectively measured profiles reflected actual changes in this patient's perception of bitter.

Following 4 weeks supplementation, the most remarkable change in nutritional status was that four out of five patients gained weight and only 1 patient lost weight. These results are very encouraging, considering all patients were weight losing at baseline and warrants further investigations. Although oedema was not evident in the group of patients, a change

in weight may reflect a shift in fluid balance that would disrupt weight patterns. Looking more closely at this weight maintenance, no changes in upper arm anthropometry were noted. Similar results have been demonstrated by Wigmore and colleagues (1996) in a group of patients whose weight was maintained over a 3 month period following omega 3 fatty acid supplementation. Likewise, patients studied by Wigmore and colleagues were weight losing (2.9kg/month) at baseline. Our current results support the evidence that omega 3 fatty acids play an important role in the attenuation of weight loss associated with an acute phase response.

In healthy human studies the consumption of dietary fat supplements constitutes only a small amount of total energy intake. Whereas, in patients with reduced dietary intakes associated with advanced cancer, dietary fat supplements may contribute significantly to the total energy intake. However, this contribution to dietary intake may not attenuate the weight loss in patients with an acute phase response and an elevation of pro-inflammatory cytokines.

8.4.3 Intervention: compliance and effects

The analysis of plasma cytokines highlights interesting findings where following intervention, no changes in plasma TNF α levels were found. In only one patient, plasma levels of IL-1 and IL-6 were lowered following supplementation and remained elevated in other patients. It must be considered that continuous changes in cytokine levels attributed to an advanced stage of disease, may be masked by changes attributed to the effects of the intervention study. Measures could not be taken to control for these possible changes. It

would be interesting to examine the cytokine levels over a longer period. This would provide an indication of the changes in cytokine levels reflective of a dynamic disease process.

The analysis of plasma cytokines raises two important questions, firstly, whether compliance to the omega 3 fatty acid supplements was adhered to. Secondly, these findings prompt us to examine the mechanisms of fatty acid uptake in the plasma membrane of patients with advanced cancer.

With regard to compliance, procedures were taken to ensure patient compliance was maximised without compromising QOL. The number of fish oil capsules taken was assessed on a weekly basis and Day Hospice patients completed a diary of supplements consumed. For in-patients, capsules were prescribed during routine drug rounds and monitored by staff on drug prescription forms. This approach proved non-invasive in checking compliance. In addition, compliance was measured by the plasma lipid profiles. This also serves as an indicator of the mechanism of fatty acid uptake in cancer patients. Results of fatty acid profiles indicated an alteration in plasma fatty acid profiles following 4 weeks intervention. Unfortunately, a wash-out period to allow plasma levels to return to baseline was not feasible due to changing medical condition of patients. However, in future studies, the inclusion of a wash-out period would be an area of interest, measurable in patients with greater prognosis. In addition, these results suggest that the mechanisms of fatty acid uptake appeared to be unaltered in this group of patients.

The mechanism underlying the suppression of the synthesis of IL-1 β and TNF α after dietary supplementation of omega 3 fatty acids remains inconclusive. A change in arachidonic acid metabolites may explain in part the reduced production of these cytokines (Endres, 1989). Endres and colleagues (1995) noted that after six weeks supplementation of 18g fish oil, IL1 β was reduced by 43%. This was indeed a larger supplementation dose and for a longer period compared to in this current study. In addition, cytokine levels were measured by the production of mononuclear cells stimulated with endotoxin. It was beyond the scope of this study to measure the *in vivo* cytokine production and to implement such large doses of fish oil.

8.4.4 Recruitment

It should be emphasised that this was the first nutritional intervention study to be undertaken in the hospice. Although recruitment in the first stage was on target, the expected numbers of patients recruited was not achieved. The reasons for this include that some patients withdrew due to the number of capsules and this group of patients were characterised by multiple symptoms associated with their progressive disease. Within the period of four weeks, subjects condition deteriorated or changed and hence excluded patients from continuing in the study. The difficulties in predicting prognosis resulted in fewer patients completing the assessments. In addition, inherent symptoms associated with certain tumour types such as strictures or dysphasia in oral or oesophageal cancers, or symptoms associated with metastatic disease such as confusion excluded patients from participating in an intervention study. Constraints in this longitudinal study were highlighted from the tracking of reasons for exclusion throughout the study.

Concerning the recruitment of patients, Day Hospice patients had fewer symptoms such as nausea and diarrhoea that would exclude them from the study. However, these patients had often received recent palliative chemotherapy or radiotherapy that was an exclusion criteria. The longitudinal nature of the study itself posed greater problems as compared to the previous cross-sectional study. These findings themselves are most interesting in relation to conducting research in the terminally ill. Recruitment and retention of subjects was highlighted as a frustrating and demanding aspect in palliative care research.

9.1 Summary

To summarise, the current findings provide substantive evidence to suggest that changes in taste perception occur in patients with advanced cancer who have not received any recent palliative chemotherapy or radiotherapy. These findings indicate a specific change in bitter perception rather than a general alteration in taste perception and is important firstly for meal production and product development. Moreover, changes in olfactory perception appear to accompany changes in taste perception. Perhaps bitter taste perception, associated with changes in dietary intake and nutritional status, may be used as a marker for nutritional assessment in patients with advanced cancer. Despite the heterogeneous nature of this group, patients with cancer had a lower threshold for the detection of salt and sour. In particular the recognition and detection thresholds of bitter was lower, indicating heightened bitter perception compared to control subjects. This suggests that the changes in taste sensitivity may be a natural phenomenon of the progression of the disease.

These results have important clinical implications that contribute to the understanding of the role that taste perception plays in the QOL of the terminally ill. The psycho-social relationship between taste perception, dietary intake and weight loss highlights altered taste perception as an important dimension in QOL of patients with advanced cancer. QOL is therefore an important outcome measurement in any intervention aiming to improve taste perception.

In this study, patients with advanced cancer illustrated a group nutritionally 'at risk'. This is clearly demonstrated by inadequate energy and macronutrient intakes and low body composition parameters found in the study population. The results highlight the impact

that altered taste perception plays in the food selection and subsequent dietary intake of these patients.

More importantly, these results suggest that cytokines may be implicated in the alteration of bitter taste perception. The association between plasma cytokine (TNF α) production, serum CRP concentration and altered bitter taste perception has been demonstrated. TNF α and IL1 β are known to act on the hypothalamus pituitary adrenal axis in addition to peripheral action (Sherry and Cerami, 1988). Intervention aimed at altering the production of TNF α and the associated CRP production may have an impact on taste perception. However, intervention using omega 3 fatty acids, in this study did not demonstrate any alteration in cytokines TNF α and IL-1 β concentration. However, in light of the changes in weight following the 4 weeks intervention period, the use of omega 3 fatty acids is very encouraging. In addition, the uptake of fatty acids in this group of patients highlight that the approach adopted successfully achieved compliance in patients receiving palliative care.

It is important to note that, the study procedures proved to be acceptable to patients and staff. This is the first study of its kind within the hospice setting and highlights the non-invasive approach taken to maintain the QOL of patients with terminal disease whilst obtaining accurate and reliable information. Patients, when asked at the end of the study, expressed an interest in contributing to this research. The feasibility of involving patients with advanced cancer in research without compromising patient autonomy is highlighted in this study.

9.2 Conclusions

The overall picture emerging is that independent of chemotherapy and radiotherapy, alterations in taste perception occur due to mechanisms associated with the disease process. More importantly, the results highlight the impact that altered taste perception have on QOL, dietary intake and food selection of patients with terminal malignant disease. Within this group, the clinical impact in terms of food choice, dietary intake and QOL has been established.

For the appropriate management of changes in taste perception, these results suggest that attention must also be paid to the heightened olfactory perception that patients experience. This may have implications in the selection of foods to minimise any negative impact that foods odours have on taste perception.

9.3 Further Considerations

This study specifically considered the influence of taste perception in a group of patients with advanced stage of malignant disease. However, due to time and financial constraints it was beyond the scope of this current study to examine the influence of specific tumour types on the degree of taste aberrations and associated weight loss. This would perhaps require a longer assessment period and the possibility of a multi-centered study.

Concerning this cancer group, the onset of taste changes were reported throughout all stages of the illness. This suggests that further investigations into the prevalence of altered taste perception may be conducted at an earlier stage of disease to increase retention of patients in the study. Such investigations may be appropriate in patients following diagnosis. However, when conducting an assessment of taste perception, periods of active

treatment may impinge on findings and not therefore facilitate such investigations.

Many lessons in conducting clinical research within the hospice setting are derived from this study. Changes in patients medical condition during the study period and the mode of intervention used in this study limited the recruitment and retention of patients. The way forward for a study of this nature are clearly twofold: firstly, in order to allow adequate recruitment of subjects, a multi-centre trial is required. Secondly the mode of intervention needs to be modified to ease compliance of the consumption of the required amount of omega 3 fatty acids. Patients were excluded due to swallowing problems and in addition, some patients were unwilling to consume the required number of capsules daily. One possible alternative is to use fish oil supplementation incorporated into food items. Alternatively, a pure source of EPA may necessitate a reduced number of capsules and may therefore constitute a more suitable mode of intervention.

In view of the paucity of the data during the intervention study, further studies are required. The findings from this current study may be used in the planning and design of future studies in this area. This intervention study is considered as a pilot study highlighting important considerations concerning the implementation of such intervention in the terminally ill patients.

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APPENDIX 1

PR/HJ

LOTHIAN

OUR REF:

YOUR REF:

13 March 1995

Miss R Pattison
Department of Dietetics and Nutrition
Queen Margaret College
Clerwood Terrace
EDINBURGH
EH12 8TS

Dear Miss Pattison

**RESEARCH APPLICATION - ALTERATION IN TASTE SENSITIVITY AND ITS
RELATIONSHIP WITH NUTRITIONAL STATUS IN MALIGNANT DISEASE**

Further to your application, I have great pleasure informing you that ethical approval for the above project has been granted.

As in accordance with all research projects, a yearly progress report is required.

I would like to wish you success in your study.

Yours faithfully



Linda Semple
Secretary, Medicine and Clinical Oncology,
Research Ethics Sub-Committee

PR/HJ



OUR REF:

YOUR REF:

20 February 1997

Miss R Pattison
Department of Dietetics and Nutrition
Queen Margaret College
Clerwood Terrace
EDINBURGH
EH12 8TS

Dear Miss Pattison

RESEARCH APPLICATION - ALTERATION IN TASTE SENSITIVITY AND ITS RELATIONSHIP WITH NUTRITIONAL STATUS IN MALIGNANT DISEASE

I have been asked to comment and give management approval on your proposed research with regard to the impact on current primary care services.

Having read your research application I am writing to confirm that I have no reservations. This management approval is given subject also to ethical approval having been granted.

I hope your research will ultimately improve the outcome for the care of patients with malignant disease.

Yours sincerely

DR PHILIP RUTLEDGE
Senior Medical Adviser

cc Linda Semple, Secretary, Medicine and Clinical Oncology,
Research Ethics Sub-Committee

APPENDIX 2

Department of Health

MEDICINES CONTROL AGENCY

Market Towers 1 Nine Elms Lane London SW8 5NQ

Telephone 0171-273 0328

Facsimile 0171-273 0443



Dr T F Benton
Medical Director
St Columba's Hospice
Boswell Road
Edinburgh EH5 3RW

Our Ref: MF 8000/7256

20 December 1996

Dear Dr Benton

THE MEDICINES (EXEMPTION FROM LICENCES) (SPECIAL CASES AND MISCELLANEOUS PROVISIONS) ORDER 1972
PRODUCT: Pikasol

I am writing in connection with your notification under the Medicines (Exemption from Licences) (Special Cases and Miscellaneous Provisions) Order 1972 which relates to a proposed trial using Pikasol supplied by Lube A/S.

The Licensing Authority does not propose to issue a direction under Article 4(2)(v) of the above order in this case. The above named supplier may therefore supply the product for the purpose outlined in your notification without a marketing authorisation or clinical trial certificate being required.

This exemption is conditional on your agreement that all serious or unexpected adverse reactions occurring during the course of the trial will be notified to the Licensing Authority at the earliest opportunity.

Your attention is drawn to the fact that your notification to the Licensing Authority under the above Order (ie 1972/1200) was not accompanied by the detailed and extensive data which is required to support a marketing authorisation or a clinical trial certificate. It must therefore be emphasised that the Licensing Authority has not positively assessed the product for safety, quality or efficacy.

You may wish to ensure that the hospital, or other appropriate, Ethics Committee is aware of the limitations of the Licensing Authority's approval of this trial.

We shall be pleased to see a copy of any report which is produced as a result of this trial.

Yours sincerely

Tina Hankin
Clinical Trials Unit

APPENDIX 3

DEPARTMENT OF DIETETICS AND NUTRITION

PATIENT INFORMATION

We are examining the how taste can influence what you eat and how it affects your everyday life. In order to carry out this study we will need to find out some information about yourself. The study will be in 3 parts:

- Questions about you usual food intake, your appetite and any recent changes in your weight
- The following measurement will be carried:

Height and Weight

Measurement of the thickness of your skin and muscle using calipers

A small painless measurement of your body composition

Blood and urine measurement of various proteins (this will involve taking any extra blood)

- Tasting

You will be asked to taste several samples of solutions which are mildly sweet, sour. Salty and bitter and to identify 10 well known odours. All the samples are perfectly safe and are components of what you would consume in your everyday diet. The time taken assessing taste and smell is likely to be about 30 minutes each day for 5 days.

If you agree to take part in this study, you are under no obligation to complete tests or the questions. You are therefore free to withdraw from the study at any time. This study will on no way effect your other medical treatment. Your help is much appreciated.

For Further Information:

Ruth Pattison
Research Dietitian
St.Columba's Hospice
Edinburgh

Queen Margaret College
Edinburgh

Nutrition and Taste Study

Patient Information

You may have recently noticed changes in the taste of food. We are hoping to look at taste changes, how this may affect your food choice and also to investigate how well-nourished people are when they come into St. Columba's .

What will you be expected to do?

In order to carry out this study we will need to find out some information about yourself. This study will be conducted over a period of 6 weeks. The time taken will be kept to a minimum to prevent you becoming overtired.

1. Questions about the changes in the taste of food that you have noticed and other factors that may affect your appetite (15-20 minutes).

2. The following simple measurements, which take a few minutes will be performed:

- Measurement of the thickness of your skin and muscle using calipers
- Blood and urine measurement of various proteins (this will involve taking extra blood).
- Height and Weight

3. Tasting - You will be asked to taste several samples of solutions which are mildly sweet, sour, salty and bitter and to identify 10 well known odours. All the samples are perfectly safe. The time taken assessing taste and smell is likely to take about 30 minutes.

You will then be asked to take 6g fish oil capsules per day for a period of 4 weeks. This will be in the form of 12 capsules (0.5g). The above measurements will then be repeated once again.

If you agree to take part in this study, you are under no obligation to complete tests or questions. You are therefore free to withdraw from the study at any time. This study will in no way effect your other medical treatment. Your help is much appreciated.

APPENDIX 4

CONSENT FORM

ASSESSMENT OF TASTE AND NUTRITIONAL STATUS

- * If you agree to take part in this study, you are under no obligation to complete either the tests or the questions. You are therefore free to withdraw from the study at any time. This study will in no way affect your other medical treatments.
- * All information is confidential. I would like to thank you very much for your co-operation with this study. Please do not hesitate to contact me if you have any queries at any stage.
- * As a matter of routine, I must ask you to sign this consent form.
- * I agree to take part in this nutritional study and I understand that I may withdraw my consent at any time.
- * The researcher, Ruth Pattison, has explained the procedures for taste detection and nutritional assessment. I understand the procedures and have had an opportunity to ask questions about my participation.
- * I agree for notice to be sent to my General Practitioner and my Hospital Consultant about my participation in this study.
- * I agree to the provision of any clinically significant information to my General Practitioner and Hospital Consultant.
- * I understand that this is non-therapeutic research from which I cannot expect to derive any benefit.

Signature of Patient

Signature of Investigator

Date

APPENDIX 5

Abbreviated Mental Test

1. Can you tell me your age? Correct / Incorrect

2. Can you tell me what time of the day it is? Correct / Incorrect

Address Recall : 42 West Street

3. Can you tell me what year this is? Correct / Incorrect

4. Can you tell me your address? Correct / Incorrect

5. Can you recognise these two people? Correct / Incorrect

6. Can you tell me your date of birth? Correct / Incorrect

7. Can you tell me the name of our present monarch? Correct / Incorrect

8. Can you tell me when the first world war began? Correct / Incorrect

9. Can you count backward from 20 to 1? Correct / Incorrect

10. Can you remember the address given earlier? Correct / Incorrect

APPENDIX 6

Quality of Life Questionnaire

Date

This questionnaire must only be used by the researcher, it is not suitable for the subjects to complete independently.

Name Project Number

Diagnosis

Have you noticed any changes in the taste of food or drink? Yes / No

Have you noticed any changes in the smell of food or drink? Yes / No

When did you first notice taste changes?

At Diagnosis	Chemotherap y	Radiotherapy	Sore Mouth	Weeks ago
1	2	3	4	5

Are your taste changes consistent?

At time more noticeable	At times less noticeable	Continuous	Getting better	Getting worse
1	2	3	4	5

Before your illness, how would you have described your appetite?

Enjoyed eating everything	Enjoyed eating most things	Ate because you had to	Fussy eater	Ate very little
1	2	3	4	5

Have the taste changes affected your eating habits?

Eat More

Eat less

Eat different
foods

Eat at different
times of the
day

No Change

1

2

3

4

5

Do you sometimes feel hungry but the taste puts you off?

All of the time

Frequently

Occasionally

No

Never feel
hungry

1

2

3

4

5

Have the taste changes affected your general enjoyment of life?

Had a
significant
negative effect

Quiet alot

A little

No change

Improved

1

2

3

4

5

Do you ever feel too tired to eat?

All of the time

Often

Occasionally

Never

Less tired than
before

1

2

3

4

5

Has your illness affected the interest you take in your appearance?

Yes, I don't
want to see
myself

Yes, I rarely
take an
interest

No, but I
should try
harder

No, just the
same

Take more
care then
before

1

2

3

4

5

Have the taste changes affected those close to you?

Yes, it has become a major worry	Yes, it has caused friction	Occasionnally it has been noticed	No	No close relationships
1	2	3	4	5

Now some more general questions about your present quality of life.

How often nowadays do you socialise with friends and / or family?

Frequently	Rarel, I am not up to it	Rarely, I am nt a very saciable person	Never, I have lost interest in being sociable	Never, sadly I find it too exhausting
1	2	3	4	5

How often have you spoken on the phone recently with friends and / or family?

Frequently	Rarely, I am not up to it	Rarely, I never did use the phone much	Never, I sadly have lost interest	Never, don't have a phone
1	2	3	4	5

Do you enjoy watching TV, or reading a newspaper?

Frequently	Some days I do and some days I don't	Rarely, I cannot concentrate	Rarely, I never did	No
1	2	3	4	5

Do you have a hobby? Yes / No Do you still enjoy it?

Yes, this has not cahnged	Some days I do and some days I don't	Rarely, I cannot concentrate	No, I have not the energy	No hobby
1	2	3	4	5

Do you ever feel tense and nervous?

Most of the time	Quite often	Only when I go to the doctors or the hospital	Very rarely	Never
1	2	3	4	5

APPENDIX 7

PATIENT NO. DATE

NAME	
SEX	M (1) F (2)
D.O.B.	
AGE	
ADMISSION DATE	
REASON FOR ADMISSION	
DIAGNOSIS	
METASTATIC DISEASE	

RELEVANT DRUG TREATMENT

[illegible]

PATIENT NO. DATE

DEMISPAN (cm)		HEIGHT (m)	
WEIGHT (kg)		DEMIQUET (M)	
		MINDEX (F)	
RECENT WEIGHT LOSS (kg)		HANDGRIP (kg)	

AC (cm)			
TSF (mm)		% TSF	
AMC (mm)		% AMC	
AMA (mm)		% AMA	

Resistance		LBM (kg)	
Reactance		TBF (kg)	
		TBW (l)	
		BCM (kg)	

Have you noticed that food / drink tastes different since you became ill?

If yes, do you find that food tastes

more sweet
less sweet
more salty
less salty
more sour
less sour
more bitter
less bitter
just tasteless

Name any foods that in particular you either:

enjoy more:

enjoy less:

Do you take any supplements eg Complian, Build-up, Vitamins?

How would you describe your appetite recently?

PATIENT NO. DATE

Food Intake

As compared to your normal intake during the past month, food intake has:

- Unchanged
- More than usual
- Less than usual

Food intake now:

- Little solid food
- Only liquid
- Very little of anything
- Normal

Symptoms

Any of the following problems that have kept you from eating:

- No problems eating
- No appetite, just do not feel like eating
- Nausea
- Constipation
- Mouth sores
- Vomiting
- Diarrhoea
- Dry mouth
- Pain

APPENDIX 8

PATIENT NO. DATE

SOLUTIONS	1 st	2 nd	3 rd	4 th
SOLUTION CODE	A1	A2	A3	A4
ANSWER				
SOLUTION CODE	B1	B2	B3	B4
ANSWER				
SOLUTION CODE	C1	C2	C3	C4
ANSWER				
SOLUTION CODE	D1	D2	D3	D4
ANSWER				

Last Meal / Snack

- O = TASTELESS
- X = TASTELESS DETECTED
- XX= TASTE RECOGNISED
- XXX = DIFFERENCES OF CONCENTRATION RECOGNITION

PATIENT NO. DATE

BOTTLE NO.	ODOUR IDENTITY
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	

APPENDIX 9

PIKASOL CLINICAL TRIAL

PRESCRIPTION

Patient Name:

Address:

Please Dispense:

Pikasol Capsules Capsules times a day for 4 weeks

Prescribers Signature

Date

APPENDIX 10

NUTRITION AND TASTE STUDY

**We would be grateful if you would complete this daily diary to record the
number of capsules taken daily and any side-effects.**

PATIENT NAME

WEEK BEGINNING

For information, please contact:

**Ruth Pattison
Research Dietitian
St.Columba's Hospice**

DAY	NO. CAPSULES TO BE TAKEN	NO. CAPSULES TAKEN TO-DAY	ANY SIDE -EFFECTS
MONDAY			
TUESDAY			
WEDNESDAY			
THURSDAY			
FRIDAY			
SATURDAY			
SUNDAY			